KDIGO CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS

Online Supplementary Tables
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Abbreviations and Acronyms for Supplementary Tables

Δ	Change	MDRD	Modification of Diet in Renal Disease
↓	Decrease	MN	Membranous nephropathy
↑	Increase	MMF	Mycophenolate mofetil
ACTH	Adrenocorticotropic hormone	MP	Methlyprednisolone
ACE-I	Angiotensin-converting enzyme inhibitors	N	Number
AE	Adverse events	N&V	Nausea and vomiting
ALP	Alkaline phosphatase	NA	Not applicable
ANCA	Anti-neutrophil cytoplasmic antibody	NaCl	Sodium chloride
ARB	Angiotensin receptor blockade	nd	Not documented
ARR	Absolute relative risk	NNT	Number needed to treat
ASN	American Society of Nephrology	NS	Not significant
AZA	Azathioprine	OR	Odds ratio
BP	Blood pressure	p.o.	Oral
CR	Complete remission	PR	Partial remission
CrCl	Creatinine clearance	Pred	Prednisone
CsA	Cyclosporine	pts	Patients
Cyc	Cyclophosphamide	RCT	Randomized controlled trial
DBP	Diastolic blood pressure	RD	Risk difference
D/C	Discontinued	RPGN	Rapidly progressive glomerulonephritis
DM	Diabetes mellitus	RR	Relative risk
eGFR	Estimated glomerular filtration rate	RRT	Renal replacement therapy
ESRD	End-stage renal disease	S_{Cr}	Serum creatinine
ESRF	End-stage renal failure	SLE	Systemic lupus erythematosus
ERT	Evidence review team	SRNS	Steroid-resistant nephritic syndrome
FRNS	Frequently relapsing nephritic syndrome	SSNS	Steroid sensitive nephritic syndrome
FSGS	Focal segmental glomerulonephritis	TAC	Tacrolimus
GFR	Glomerular filtration rate	TB	Tuberculosis
GI	Gastrointestinal	UACR	Urine albumin creatinine ratio
HbA1c	Hemoglobin A1c	UI	Unique identifier
HR	Hazards ratio	UK	United Kingdom
HSP	Henich-Schoenlein purpura	UPCR	Urine protein creatinine ratio
HSV	Herpes simplex virus	UPE	Urine protein excretion
HTN	Hypertension	US	United States
IMN	Idiopathic membranous nephropathy	UTI	Urinary tract infection
IU	International units	WGM	Work group member
i.v.	Intravenous	WMD	Weighted mean difference
LFT	Liver function test		
LN	Lupus Nephritis		

Supplementary table 1. Evidence profile of studies examining i.v. vs. p.o. Cyc treatment in children with frequently relapsing nephrotic syndrome

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	0 RCTs	--	--	--	--	--	--	--	Critical
ESRD	0 RCTs	--	--	--	--	--	--	--	Critical
Relapse	1 Non-RCT (Moderate) 1 SR (2 RCTs)	19 (10) 83 (41)	Some limitations (-1) Some limitations (-1)	No important inconsistencies (0)	Direct (0)	Sparse (-1)	Low	Benefit for monthly i.v. cyclophosphamide at 6 but not at end of study.	High
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Kidney function (categorical)	0 RCTs	--	--	--	--	--	--	--	High
ΔProteinuria (continuous)	0 RCTs	--	--	--	--	--	--	--	Moderate
ΔKidney function (continuous)	0 RCTs	--	--	--	--	--	--	--	Moderate
Adverse events	1 Non-RCT (Moderate) 1 SR (1 RCT)	19 (10) 48 (26)	Some limitations (-1) Some limitations (-1)					More nausea and vomiting with i.v. cyclophosphamide; more infections with p.o. cyclophosphamide.	Moderate

Balance of potential benefits and harm:
No difference between monthly i.v. cyclophosphamide and oral cyclophosphamide

Quality of overall evidence:
Low

Supplementary table 2. Existing systematic reviews on i.v. vs. p.o. Cyc treatment in children with frequently relapsing nephrotic syndrome

Study, Year, RefID	Study Eligibility Criteria	Interventions (Studies)	Outcomes	Conclusions	Comments	Yes/No
Hodson[34] Date Base: CENTRAL(Cochrane Renal Group), MEDLINE and EMBASE Search Dates: Central: (Sept 2007) Medline: (1966-Sept 2007) EMBASE: (1980-Sept 2007) N Studies: 26 trials included in this update N Subjects: 1173 children	Inclusion: 1) Children aged three months to 18 years with relapsing SSNS (i.e. the child became oedema-free and his/her urine protein was = 1+ on dipstick or <4 mg/m²/h for three consecutive days while receiving corticosteroid therapy). Relapse of nephritic syndrome is defined as the recurrence of proteinuria measured semi-quantitatively on urine analysis or quantitatively using albumin or protein to creatinine ratios or timed urine specimens. A renal biopsy diagnosis of minimal change disease was not required. Exclusion: 1) First episode of SSNS 2) Steroid-resistant nephritic syndrome 3) Other renal or systemic forms of nephritic syndrome defined on renal biopsy, clinical features or serology (e.g. post-infectious glomerulonephritis, Henoch-Schonlein nephritis, systemic lupus erythematosus).	1. i.v. vs. oral cyclophosphamide regimens (Abeyagunawardena 06b; Prasad 2004) Other interventions were included in the meta-analysis and are the subject of other summary tables	# children relapse within 6 months # children relapse within 12-24 months Mean relapse rate/pt/y Adverse Events: HTN Leukopenia Infections Alopecia N&V/ GI	Oral or i.v. cyclophosphamide, oral chlorambucil, cyclosporin and levamisole substantially reduce the incidence of relapse in children with relapsing SSNS. The benefit of non-corticosteroid agents is sustained beyond the on-treatment period for the alkylating agents but rarely with cyclosporin and levamisole. However there are inadequate data available to determine which agent should be preferred initially. Thus the decision as to which medication should be used in a child with frequently relapsing or steroid dependent SSNS will largely depend on patient and physician preference following discussion of the possible side effects and the costs of courses of alkylating agents and those of prolonged courses of cyclosporin or levamisole. Clinically important differences in efficacy are possible and further comparative studies are still needed.	Is eligibility criteria similar to the guideline Are there any limitations to systematic review methodology Is limitation to evidence clearly addressed by the authors	Yes No Yes
Description of limitations of evidence by authors		Small sample size				

Author, Year, RefID	Intervention	Control	Outcome	N studies (N intervention group/ total N)	Pooled RR (95% CI)	P-value	Test for heterogeneity	
							I^2 Statistic (%)	P-value
Hodson 2008[34]	i.v. Cyc	p.o. Cyc	Relapse within 6 months	2 (41/83)	0.54 [0.34, 0.88]	0.01	0	0.82
	i.v. Cyc	p.o. Cyc	Continuing FRNS or SDNS at 6 months	1 (26/47)	0.40 [0.18, 0.89]	nd	NA	NA
	i.v. Cyc	p.o. Cyc	Relapse by end of study	2 (41/83)	0.99 [0.76, 1.29]	0.9	0	0.86
	i.v. Cyc	p.o. Cyc	AE: All infections	2 (41/83)	0.14 [0.03, 0.72]	nd	NA	NA
	i.v. Cyc	p.o. Cyc	AE: Leukopenia	2 (41/83)	0.37 [0.09, 1.51]	nd	NA	NA
	i.v. Cyc	p.o. Cyc	AE: Hair Loss	2 (41/83)	0.19 [0.04, 1.03]	nd	NA	NA
	i.v. Cyc	p.o. Cyc	AE: Nausea & Vomiting	2 (41/83)	4.07 [0.21, 80.51]	nd	NA	NA

Supplementary table 3. Summary tables of studies examining i.v. vs. p.o. Cyc treatment in children with frequently relapsing nephrotic syndrome (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		P value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
Relapse												
Patients without a relapse	Bircan 2003[8] Turkey	2 y (12 wk)	i.v. Cyc and prednisone	p.o. Cyc and prednisone	10 (10)	9 (9)	nd	nd	5 (50%) [3 (33%)]	RR 1.50 (0.49-4.56)[1]	<0.05	Fair
Adverse events												
AE-oral thrush	Bircan 2003[8] Turkey	2 y (12 wk)	i.v. Cyc and prednisone	p.o. Cyc and prednisone	10 (10)	9 (9)	nd	nd	0% [22%]	--	nd	Fair
AE-upper respiratory infections									0% [22%]	--	nd	Fair

[1] Calculated by ERT

Supplementary table 4. Summary table of RCT examining MMF vs. CsA in frequently relapsing nephrotic syndrome in children (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			No. Events (%) Intervention [Control]	RR		
Relapse												
No relapses	Dorresteijn 2008[21] Netherlands and Belgium	12 mo (12 mo)	MMF	CsA	12 (15)	12 (16)	GFR 125 ml/min/1.73 m^2	nd	5 (42%) [1 (8%)]	5.0 (0.68, 36.66)	NS	Fair
Adverse events												
AE-diarrhea	Dorresteijn 2008[21] Netherlands and Belgium	12 mo (12 mo)	MMF	CsA	12 (15)	12 (16)	GFR 125 ml/min/1.73 m^2	nd	0 (0%) [0 (0%)]	--	--	Poor
AE-HTN									1 (8%) [4 (33%)]	0.25 (0.03-1.92)	NS	Poor
AE-Leukopenia[2]									0 (0%) [0 (0%)]	--	--	Poor
AE-hypertrichosis									0 (0%) [3 (38%)]	--	nd	Poor
AE- Gingival Hyperplasia									0 (0%) [6 (60%)]	--	nd	Poor

[2] Leucocytes <4.0×1000 cells/mm^3 in >1 measurement.

Supplementary table 5. Summary table of RCT examining MMF vs. cyclosporine in frequently relapsing nephrotic syndrome in children (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Relapse													
Relapse Rate	Dorresteijn 2008[21] Netherlands and Belgium	12 mo (12 mo)	MMF	CsA	12 (15)	12 (16)	GFR 125 ml/min/1.73 m^2	nd	per patient-year	--	0.83 (0.08)	NS (0.08)	Fair
Kidney function													
ΔGFR	Dorresteijn 2008[21] Netherlands and Belgium	3 mo (12 mo)	MMF	CsA	12 (15)	12 (16)	GFR 125 ml/min/1.73 m^2	nd	ml/min/ 1.73 m^2	125 (123)	-2 (-11)	0.03	Poor
		6 mo (12 mo)									+1 (-16)		
		9 mo (12 mo)									0 (-9)		
		12 mo (12 mo)									+6 (-14)		

Supplementary table 6. Summary table of RCT examining low vs. fixed dose CsA treatment in children with frequently relapsing nephrotic syndrome (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention[2]	Control[2]	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
Sustained remission												
In all patients	Ishikura 2008[41] Japan	24 mo (24 mo)	Low dose CsA	Fixed dose CsA	24 (29)	20 (27)	nd	nd	50% [15%]	HR 0.37 (0.18–0.79)	0.01	Good
Among patients without relapse during first 6 mo					23 (29)	19 (27)			57% [25%]	HR 0.43 (0.17–1.09)	NS (0.08)	Good
Biopsy results												
Mild arteriolar hyalinosis	Ishikura 2008[41] Japan	24 mo (24 mo)	Low dose CsA	Fixed dose CsA	20 (29)	15 (27)	nd	nd	4 (20%) [1 (7%)]	RR 3.0 (0.37-24)	NS	Poor
Striped fibrosis or tubular atrophy									0% [0%]	--	--	Poor
Adverse events[3]												
AE-HTN	Ishikura 2008[41] Japan	24 mo (24 mo)	Low dose CsA	Fixed dose CsA	24 (29)	20 (27)	nd	nd	25% [10%]	RR 2.5 (0.57-11)	NS (0.20)	Fair
AE-hypertrichosis									17% [15%]	RR 1.11 (0.28-4.4)	NS	Poor
AE- gingival hyperplasia									8% [20%]	RR 0.42 (0.08-2.0)	NS	Poor

[3] Also no difference in headache, gastric pain, elevation of ALP, hyperuricemia, transient elevation of S_{Cr}.

[2] All patients received 6 months of cyclosporine targeting a trough level of 80-100 ng/ml. In the subsequent 18 months, patients randomized to low dose had their dose adjusted to maintain trough cyclosporine levels 60-80 ng/mL while those randomized to fixed dose received 2.5mg/kg/day

Supplementary table 7. Summary table of RCT examining low vs. fixed dose CsA treatment in children with frequently relapsing nephrotic syndrome (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Relapse Rates													
Per patient year	Ishikura 2008[41] Japan	24 mo (24 mo)	Low dose CsA	Fixed dose CsA	24 (29)	20 (27)	nd	nd	--	3.1 (3.6)	-2.76 (-2.67)	nd	Good
Rate of progression to FRNS													
Per patient year	Ishikura 2008[41] Japan	24 mo (24 mo)	Low dose CsA	Fixed dose CsA	24 (29)	20 (27)	nd	nd	--	--	0.14 (0.42)	nd	Good
Height													
Mean s.d. score for height	Ishikura 2008[41] Japan	24 mo (24 mo)	Low dose CsA	Fixed dose CsA	23 (29)	17 (27)	nd	nd	--	-0.70 (-0.62)	+0.60 (+0.58)	nd	Fair

Supplementary table 8. Evidence profile of RCTs examining CsA vs. placebo in steroid-resistant nephrotic syndrome in children

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	0 RCTs	--	--	--	--	--	--	--	Critical
ESRD	0 RCTs	--	--	--	--	--	--	--	Critical
Remission	3 RCTs[4] (High)	49 (26)	No limitations[5] (0)	No important consistencies (0)	Direct (0)	Sparse (-1)	Moderate	Benefit of cyclosporine for complete remission as compared with placebo or no treatment	High
Relapse	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Kidney function (categorical)	0 RCTs	--	--	--	--	--	--	--	High
ΔProteinuria (continuous)	0 RCTs	--	--	--	--	--	--	--	Moderate
∆Kidney function (continuous)	0 RCTs	--	--	--	--	--	--	--	Moderate
Adverse events	3 RCTs[6] (High)	49 (26)						No nephrotoxicity or hirsuitism reported although these are well known side effects of cyclosporine. These studies involved small numbers.	Moderate
Balance of potential benefits and harm: Benefit of cyclosporine in inducing complete remission							**Quality of overall evidence:** Moderate		

[4] One of the RCTs has only been published in abstract form (Ponticelli 1993a) but was included in the Cochrane Systematic Review (Hodson 2006[33])
[5] The quality of the trials is based on the evaluation performed in the systematic review (Hodson 2006), not the independent review of trials by the ERT.
[6] One of the RCTs has only been published in abstract form but was included in the Cochrane Systematic Review (Ponticelli 1993a)

Supplementary table 9. Meta-analyses and systematic reviews on steroid-resistant nephrotic syndrome in children

Study, Year, RefID	Study Eligibility Criteria	Interventions (Studies)	Outcomes	Conclusions	Comments	Yes/No
Hodson 2006[33] Database: Cochrane (central) Search Dates: This is an update to original search performed Cochrane (2002, issue 2) Medline 1966 – April 2002 Embase 1980-April 2002 Updated with Cochrane Central Registry up to Jun 2005 N Studies: 11 N Subjects: 312	**Inclusion criteria** Children aged three months to 18 years with corticosteroid-resistant nephrotic syndrome (i.e. persistent proteinuria ≥3+ on dipstick, urinary protein-creatinine ratio >0.2 g/mmol or >40 mg/m²/h after four weeks or more of daily corticosteroid agent). Where a renal biopsy was performed, only children with biopsy diagnoses of MCNS, MPGN or FSGS were included. **Exclusion criteria** steroid-responsive nephrotic syndrome, congenital nephrotic syndrome or other renal or systemic forms of nephrotic syndrome defined on renal biopsy, clinical features or serology (e.g. post-infectious glomerulonephritis, Henoch-Schönlein nephritis, systemic lupus erythematosus, membranous glomerulopathy or mesangiocapillary glomerulonephritis)	1) Cyclosporine vs. placebo/no treatment (Garin 1988, Lieberman 1996, Ponticelli 1993a)	1) Complete remission during and following therapy (i.e. oedema free and urine protein was <1+ on dipstick, urine protein-creatinine <0.02 g/mmol or <4mg/m²/h for three or more consecutive days). **Secondary outcomes** • Partial remission with reduction in proteinuria (i.e. proteinuria <2+ , urine protein-creatinine ratio <0.2 g/mmol or <40 mg/m²/h) and an increase in serum albumin levels. • Changes in renal function (serum creatinine, creatinine clearance) • Number reaching end stage renal failure • Adverse effects of therapy	1) Cyclosporine when compared with placebo or no treatment significantly increased the number who achieved complete remission	Is eligibility criteria similar to the guideline	Yes
					Are there any limitations to systematic review methodology	No
					Is limitation to evidence clearly addressed by the authors	Yes
Description of limitations of evidence by authors	Trials were generally small and of variable quality. Large confidence intervals – uncertainty in summary estimates. Most trials did not provide data on the duration of remission, on renal dysfunction, the number progressing to end stage renal failure or mortality.					

Author, Year, RefID	Intervention	Control	Outcome	N studies (N intervention group/ total N)	Pooled RR[1] (95% CI)	*P*-value	Test for heterogeneity		Grading of Reference
							I^2 Statistic	*P*-value	
Hodson 2006[33]	Cyclosporine	Placebo/ no treatment	Failure to achieve complete remission (all pathologies)	3 26/49	0.66 [0.48, 0.91]	0.012	0	0.82	Garin 1988, Poor Lieberman 1996 Fair Ponticelli 1993a Fair
	Cyclosporine	Placebo/ no treatment	Failure to achieve complete remission (FSGS only)	2 16/33	0.70 [0.50, 0.99]	0.045	0	0.76	
	Cyclosporine	Placebo/ no treatment	Failure to achieve complete or partial remission (all pathologies)	3 26/49	0.18 [0.01, 3.32]	0.25	77.0	0.04	
	Cyclosporine	Placebo/ no treatment	Failure to achieve complete or partial remission (FSGS)	1 12/24	0.05 [0.00, 0.73]	0.029	NA	NA	

Supplementary table 10. Evidence profile of studies examining CsA vs. Cyc treatment in children with steroid-resistant nephrotic syndrome

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	0 RCTs	--	--	--	--	--	--	--	Critical
ESRD	1 Non-RCT (Moderate)	14 (4)	Serious limitations (-2)	NA	Direct (0)	Sparse (-1)	Very low	Insufficient evidence	Critical
Remission	1 RCT (High) 1 Non-RCT (Moderate)	32 (15) 14 (4)	Some limitations (-1) Serious limitations (-2)	No important inconsistencies (0)	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Possible benefit for CsA for remission at 12 weeks.	High
Relapse	1 Non-RCT (Moderate)	14 (4)	Serious limitations (-2)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Insufficient evidence	High
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Kidney function (categorical)	0 RCTs	--	--	--	--	--	--	--	High
ΔProteinuria (continuous)	0 RCTs	--	--	--	--	--	--	--	Moderate
ΔKidney function (continuous)	0 RCTs	--	--	--	--	--	--	--	Moderate
Adverse events	0 RCTs	--						--	Moderate

Balance of potential benefits and harm:
Insufficient evidence

Quality of overall evidence:
Very low

Supplementary table 11. Summary table of studies examining CsA vs. Cyc treatment in children with steroid-resistant nephrotic syndrome (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR		
RRT												
Renal failure	Hafeez 2005[31] India	12 mo (12 wk)	CsA[7]	Cyc[8]	4 (4)	10 (10)	nd	>40 mg/m^2/hr	0 (0%) [0 (0%)]	--	nd	Poor
Remission												
Complete	Plank 2008[62] Germany, Austria	12 wk (48 wk)	CsA[9]	i.v. Cyc[10]	15 (15)	17 (17)	GFR 191 ml/min/1.73 m^2	217 mg/m^2/h	2 (13%) [1 (6%)]	RR 2.3 (0.23-23)[11]	NS (0.58)	Fair
Partial									7 (47%) [2 (12%)]	nd[12]	0.04	Fair
Complete or Partial									9 (60%) [3 (18%)]	nd[13]	0.03	Fair
Complete		24 wk (48 wk)			13 (15)	6 (17)			2 (15%) [1 (17%)]	RR 0.92 (0.10-8.3) [14]	NS	Poor
Partial									9 (69%) [3 (50%)]	RR 1.38 (0.58-3.3) [15]	NS	Poor
Complete or Partial									11 (85%) [4 (67%)]	RR 1.27 (0.69-2.3) [16]	NS	Poor
Complete		48 wk (48 wk)			10 (15)	3 (17)			2 (20%) [2 (67%)]	RR 0.3 (0.07-1.31) [17]	NS	Poor
Partial									8 (80%) [1 (33%)]	RR 1.20 (0.51-2.83) [18]	NS	Poor
Complete or partial									10 (100%) [3 (100%)]	RR 1.00 (1.00-1.00) [19]	--	Poor
Complete	Hafeez 2005[31] India	12 mo (12 wk)	CsA	Cyc	4 (4)	10 (10)	nd	>40 mg/m^2/hr	3 (75%) [5 (50%)]	RR 1.50 (0.65-3.47) [20]	NS	Poor
Partial									1 (25%) [1 (10%)]	RR 2.50 (0.20-31.00) [21]	nd	Poor

[7] CsA 7-10 mg/kg/d in 2 divided doses X 12 mo
[8] p.o. cyclophosphamide 2.5 mg/kg/d X 12 wk
[9] Sandimmune targeting a trough level of 150 ng/mL X 12 wk and if proteinuria remained >40 mg/m^2/h targeted a cyclosporine trough level of 350 ng/mL x 12 wk
[10] IV Cyclophosphamide 500-1000 mg/m^2 monthly X 12 wk and if proteinuria >40 mg/m^2/h treated with IV MP pulses repeated monthly x 12 wk
[11] Calculated by ERT
[12] Not calculated since confidence intervals of calculated relative risk is not significant however, reported p values from published article show significance. This probably due to an adjusted analysis that was not described.
[13] Not calculated since confidence intervals of calculated relative risk is not significant however, reported p values from published article show significance. This probably due to an adjusted analysis that was not described.
[14] Calculated by ERT
[15] Calculated by ERT
[16] Calculated by ERT
[17] Calculated by ERT
[18] Calculated by ERT
[19] Calculated by ERT
[20] Calculated by ERT
[21] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR		
Complete or partial									4 (100%) [5 (50%)]	RR 2.00 (1.08-3.72) [22]	nd	Poor
Relapse												
After treatment	Hafeez 2005[31] India	12 mo (12 wk)	CsA	Cyc	4 (4)	10 (10)	nd	>40 mg/m^2/hr	1 (25%) [0 (0%)]	--	nd	Poor

[22] Calculated by ERT

Supplementary table 12. Evidence profile of RCTs examining ACE-I treatment for steroid-resistant nephrotic syndrome in children

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	0 RCTs	--	--	--	--	--	--	--	Critical
ESRD	0 RCTs	--	--	--	--	--	--	--	Critical
Remission	0 RCTs	--	--	--	--	--	--	--	High
Relapse	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Kidney function (categorical)	0 RCTs	--	--	--	--	--	--	--	High
ΔProteinuria (continuous)	2 RCTs (High)	95 (50)	No limitations (0)	No important consistencies (0)	Direct (0)	Sparse (-1)	Moderate	Benefit of ACE-I; high dose greater than low dose greater than placebo	Moderate
∆Kidney function (continuous)	1 RCT (High)	45 (25)	No limitations (0)	N/A	Direct (0)	Sparse (-1)	Moderate	Insufficient evidence	Moderate
Adverse events	0 RCTs	--						--	Moderate

Balance of potential benefits and harm:
Benefit of ACE-I

Quality of overall evidence:
Moderate

Supplementary table 13. Summary table of RCTs examining ACE-I treatment for steroid-resistant nephrotic syndrome in children (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
24 h Proteinuria	Yi 2006[88] China	4 wk (12 wk)	Fosinopril + prednisone	Prednisone	25 (30)	20 (27)	S_{Cr} 0.56 mg/dl	3.94 g/d	g/d	3.94 (4.44)	-2.69 (-1.92)	<0.05	Good
		12 wk (12 wk)									-2.84 (-2.39)		Good
Median % reduction in UACR (low to high dose)	Bagga 2004[5] India	2-10 wk (8 wk)	Enalapril 0.2 to 0.6 mg/kg/d [Low to high dose]	Enalapril 0.6 to 0.2 mg/kg/d [High to low dose]	25 (25)	25 (25)	S_{Cr} 0.6 mg/dl	UACR 3.9	%	NA	34.8 (-7.9 to 76.6)	nd	Good
Median % reduction in UACR (low to high dose)		12-20 wk (8 wk)									37.2 (11.3–59.8)	nd	Good
Median % reduction in UACR (high to low dose)		2-10 wk (8 wk)									62.9 (40.6–71.6)	nd	Good
Median % reduction in UACR (high to low dose)		12-20 wk (8 wk)									33.3 (-20 to 58.7)	nd	Good
S_{Cr}/GFR/CrCl													
CrCl	Yi 2006[88] China	12 wk (12 wk)	Fosinopril + prednisone	Prednisone	25 (30)	20 (27)	S_{Cr} 0.56 mg/dl	3.94 g/d	ml/min/ 1.73 m^2	91.3 (96.1)	-2.51 (-2.03)	NS	Good

Supplementary table 14. Evidence profile of studies of p.o. Cyc plus steroid vs. steroid in steroid-resistant nephrotic syndrome and/or FSGS in children

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	1 RCT (High)	60 (35)	Some limitations[23] (-1)	N/A	Direct (0)	Sparse (-1) Imprecision (-1)	Very Low	No difference	Critical
ESRD	2 Non-RCTs (Moderate)	70 (40)	Serious limitations[24] (-2)	No important inconsistencies (0)	Direct (0)	Sparse (-1)	Very Low	No difference	Critical
Remission	2 RCTs (High)	93 (53)	Some limitations[25] (-1)	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	No difference	High
	2 Non-RCTs (Moderate)	70 (40)	Serious limitations[26] (-2)						
Relapse	0 RCTs	--	--	--	--	--	--	--	
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	
Progression of kidney disease[27]	1 RCT (High)	60 (35)	Some limitations[28] (-1)	Some inconsistencies (-1)	Direct (0)	None (0)	Low	No difference	Moderate
	1 Non-RCT (Moderate)	54 (30)	Serious limitations[29] (-2)						
ΔProteinuria (continuous)	0 RCTs	--	--	--	--	--	--	--	
Kidney function (continuous)	0 RCTs	--	--	--	--	--	--	--	
Adverse events	2 RCTs	93 (53)	Some limitations[30] (-1)					Alopecia, hemorrhagic cystitis, leucopenia, infections more likely with cyclophosphamide	Moderate
	2 Non-RCTs	70 (40)	Some limitations[31] (-1)						

[23] The quality of the trials is based on the evaluation performed in the systematic review (Hodson 2006), not the ERT's independent review of the trials.
[24] The quality of the trials is based on the evaluation performed in the systematic review (Hodson 2006), not the ERT's independent review of the trials.
[25] The quality of the trials is based on the evaluation performed in the systematic review (Hodson 2006), not the ERT's independent review of the trials.
[26] The quality of the trials is based on the evaluation performed in the systematic review (Hodson 2006), not the ERT's independent review of the trials.
[27] Defined in the RCT as increase in serum creatinine from baseline of ≥30% or >0.4 mg/dl or onset of renal failure as evidenced by serum creatinine >4.0 mg/dl, maintenance on chronic dialysis, or renal transplantation; not defined in the NRCS
[28] The quality of the trials is based on the evaluation performed in the systematic review (Hodson 2006), not the ERT's independent review of the trials.
[29] The quality of the trials is based on the evaluation performed in the systematic review (Hodson 2006), not the ERT's independent review of the trials.
[30] The quality of the trials is based on the evaluation performed in the systematic review (Hodson 2006), not the ERT's independent review of the trials.
[31] The quality of the trials is based on the evaluation performed in the systematic review (Hodson 2006), not the ERT's independent review of the trials.

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Balance of potential benefits and harm: No difference; more adverse effects with cyclophosphamide							**Quality of overall evidence:** Moderate		

Supplementary table 15. Summary table of studies examining p.o. Cyc plus steroid vs. steroid in children with SRNS or FSGS. Based on data reported in Hodson 2006. (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR		
Mortality												
12 mo	Tarshish 1996[82] US	12 mo (12 mo)	p.o. Cyc and p.o. prednisone	Prednisone	35 (35)	25 (25)	GFR 118 ml/min	161 mg/m^2/h	3 (9%) [2 (10%)]	RR 0.98 (0.18-5.40) [32]	NS (>0.1)	Fair
ESRD												
12 mo	Hafeez 2005[31] India	12 mo (12 mo)	p.o. Cyc x 12 wk p.o. steroids x 12 mo	Methyl-prednisolone [33] >12 mo + p.o. prednisone >12 mo	10 (10)	6 (6)	nd	>40 mg/m^2/hr	0 (0%) [1 (17%)[34]]	--	nd	Poor
86 mo	Martinelli 2004[55] Brazil	86 mo (4 mo)	p.o. Cyc and p.o. prednisone	p.o. prednisone	30 (30)	24 (24)	nd	nd	3 (10%) [6 (25%)]	RR0.40 (0.11-1.44) [35]	NS (>0.1)	Poor
Remission												
Complete	Tarshish 1996[82] US	12 mo (12 mo)	p.o. Cyc and p.o. prednisone	Prednisone	32 (35)	21 (25)	GFR 118 ml/min	161 mg/m^2/hr	8 (25%) [6 (28%)]	RR0.88 (0.35-2.16) [36]	NS (>0.1)	Fair
Complete	ISKDC 1974[1] EU, North America	24 mo (90 days)	p.o. Cyc and p.o. prednisone	Prednisone	18 (18)	15 (15)	nd	>40 mg/m^2/h	10 (56%) [6 (40%)]	RR 1.39 (0.66-2.93) [37]	NS (>0.05)	Fair
Complete remission	Hafeez 2005[31] India	12 mo (12 mo)	p.o. Cyc x 12 wk p.o. steroids x 12 mo	Methyl-prednisolone [38] >12 mo + p.o. prednisone >12 mo	10 (10)	6 (6)	nd	>40 mg/m^2/hr	5 (50%) [2 (33%)]	RR 1.50 (0.41-5.45)[39]	NS (0.54)	Poor
Partial remission									1 (10%) [1 (17%)]	RR 0.60 (0.05-7.92)[40]	NS (0.698)	
Complete remission	Martinelli 2004[55] Brazil	86 mo (4 mo)	p.o. Cyc and p.o. prednisone	p.o. prednisone	30 (30)	24 (24)	nd	nd	8 (27%) [3 (13%][41])	RR 2.13 (0.63-7.18) [42]	NS	Poor
Partial remission									6 (20%) [2 (8%)[43]]	RR 2.40 (0.53-10.84) [44]	NS	Poor

[32] Calculated by ERT
[33] Some converted partially or fully to oral steroids. Cyclophosphamide added if "response was not satisfactory".
[34] Showed no response to therapy. Had FSGS. "Developed renal failure over a period of 1 year."
[35] Calculated by ERT
[36] Calculated by ERT
[37] Calculated by ERT
[38] Some converted partially or fully to oral steroids. Cyclophosphamide added if "response was not satisfactory".
[39] Calculated by ERT
[40] Calculated by ERT
[41] The data reported in the article appear to be for combined (Prednisone alone) + (Cyc + Pred). These numbers are derived from subtracting (Cyc + Pred) from "Prednisone".
[42] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR		
Progression of Renal Disease[16]												
12 mo	Tarshish 1996[82] US	12 mo (12 mo)	p.o. Cyc and p.o. prednisone	Prednisone	35 (35)	25 (25)	GFR 118 ml/min	161 mg/m^2/hr	20 (57%) [9 (36%)]	RR 1.59 (0.87-2.88)[45]	NS (>0.1)	Fair
86 mo	Martinelli 2004[55] Brazil	86 mo (4 mo)	p.o. Cyc and p.o. prednisone	p.o. prednisone	30 (30)	24 (24)	nd	nd	5 (17%) [8 (33%)]	RR 0.50 (0.19-1.33)[46]	NS	Poor

[43] The data reported in the article appear to be for combined (Prednisone alone) + (Cyc + Pred). These numbers are derived from subtracting (Cyc + Pred) from "Prednisone".
[44] Calculated by ERT
[45] Calculated by ERT
[46] Calculated by ERT
[16] Defined as increase in serum creatinine from baseline of ≥30% or >0.4 mg/dl or onset of renal failure as evidenced by serum creatinine >4.0 mg/dl, maintenance on chronic dialysis, or renal transplantation.

Supplementary table 16. Summary table of studies examining p.o. Cyc plus steroid vs. steroid in children with SRNS or FSGS (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Time to Remission													
2 years	ISKDC 1974[1] EU, North America	2 y (90 d)	p.o. Cyc	Prednisone	18 (18)	15 (15)	nd	nd	d	NA	38.4 (95.5)	<0.05	Fair

Supplementary table 17. Summary table RCT examining i.v. vs. p.o. Cyc treatment in children with steroid-resistant nephrotic syndrome (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
Median UPCR	Mantan 2008[54] India	6mo (18 mo)	i.v. Cyc	p.o. Cyc	26 (27)	23 (25)	GFR 101 ml/min/1.73 m^2	UPCR 5.9 mg/mg	mg/mg	5.9 (8.9)	-4.3 (-4.4)	NS (0.2)	Poor
S_{Cr}/GFR/CrCl													
Median GFR	Mantan 2008[54] India	6 mo (18 mo)	i.v. Cyc	p.o. Cyc	26 (27)	23 (25)	GFR 101 ml/min/1.73 m^2	UPCR 5.9 mg/mg	ml/min/1.73 m^2	101 (107)	+2 (0)	NS (0.2)	Poor
Serum Albumin													
Median serum albumin	Mantan 2008[54] India	6 mo (18 mo)	i.v. Cyc	p.o. Cyc	26 (27)	23 (25)	GFR 101 ml/min/1.73 m^2	UPCR 5.9 mg/mg	g/dl	2.2 (1.7)	+1.8 (+1.9)	NS (0.7)	Poor

Supplementary table 18. Summary table of RCT examining TAC vs. CsA treatment in children with steroid-resistant nephrotic syndrome (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR		
Remission												
Complete remission	Choudhry 2009[14] India	6 mo (12 mo)	Tacrolimus	CsA	21 (21)	20 (20)	GFR 105 ml/min S_{Cr} 0.56 mg/dl	UPCR 9.8 g/g	43% [50%]	0.85 (0.44-1.65)	NS (0.6)	Fair
Partial remission									43% [30%]	1.42 (0.62-3.2)	NS (0.4)	Fair
Complete or partial remission									86% [80%]	1.07 (0.81-1.41)	NS (0.6)	Fair
Complete remission		12 mo (12 mo)							48% [55%]	0.86 (0.47-1.57)	NS (0.6)	Fair
Partial remission									38% [20%]	1.90 (0.67-5.34)	NS (0.2)	Fair
Complete or partial remission									86% [75%]	1.14 (0.84-1.55)	NS (0.4)	Fair
Relapse after achieving remission									11% [50%]	0.22 (0.06-0.90)	0.03	Fair
Nephrotoxicity												
Persistent	Choudhry 2009[14] India	12 mo (12 mo)	Tacrolimus	CsA	21 (21)	20 (20)	GFR 105 ml/min S_{Cr} 0.56 mg/dl	UPCR 9.8 g/g	5% [10%]	0.48 (0.05-4.9)	NS (0.5)	Fair
Reversible									33% [50%]	0.67 (0.32-1.41)	NS (0.3)	Fair
Adverse Events												
AE-worsening of HTN	Choudhry 2009[14] India	12 mo (12 mo)	Tacrolimus	CsA	18 (21)	16 (20)	GFR 105 ml/min S_{Cr} 0.56 mg/dl	UPCR 9.8 g/g	10% [0%]	0.89 (0.14-5.6)	NS (0.9)	Fair
AE-hypertrichosis									0% [95%]	--	<0.001	Fair
AE-gingival hyperplasia									5% [60%]	0.07 (0.01-0.51)	<0.001	Fair
AE-diarrhea									29% [5%]	5.3 (0.72-40)	NS	Fair
AE-sepsis/ pneumonia									5% [5%]	0.89 (0.06-13)	NS (0.9)	Fair
AE-headache									0% [5%]	--	NS (0.3)	Fair
AE-paresthesia									0% [5%]	--	NS (0.3)	Fair

Supplementary table 19. Summary table of RCT examining TAC vs. CsA treatment in children with steroid-resistant nephrotic syndrome (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
UPCR	Choudhry 2009[14] India	12 mo (12 mo)	Tacrolimus	CsA	19 (21)	16 (20)	GFR 105 ml/min S_{Cr} 0.56 mg/dl	UPCR 9.8 g/g	g/g	9.8 (8.0)	-9.3 (-7.4)	NS (0.8)	Fair
Scr/GFR/CrCl													
12 mo	Choudhry 2009[14] India	12 mo (12 mo)	Tacrolimus	CsA	19 (21)	16 (20)	GFR 105 ml/min S_{Cr} 0.56 mg/dl	UPCR 9.8 g/g	g/dl	0.56 (0.51)	+0.12 (+0.12)	NS (0.3)	Fair
Schwartz GFR									ml/min/1.73 m^2	104.6 (115.5)	-14.4 (-12%) [-16.2 (-11%)]	NS (0.1)	Fair
Albumin													
12 mo	Choudhry 2009 [14] India	12 mo (12 mo)	Tacrolimus	CsA	19 (21)	16 (20)	GFR 105 ml/min S_{Cr} 0.56 mg/dl	UPCR 9.8 g/g	g/dl	1.8 (1.6)	+2.6 (+2.3)	NS (0.08)	Fair

Supplementary table 20. Summary table of RCT examining CsA vs. steroid treatment after first relapse in adults with minimal change disease (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR		
Remission												
Complete remission	Eguchi 2010[23] Japan	2 wk (6 mo)	CsA + prednisolone	Prednisolone	26 (26)	26 (26)	S_{Cr} 0.9 mg/dl	6.7 g/d	20 (77%) [11 (42%)]	RR 1.82[47] (1.11-2.99)	0.02	Fair
		4 wk (6 mo)							25 (96%) [20 (77%)]	RR 1.25[48] (1.00-1.56)	nd	
		3 mo (6 mo)							24 (92%) [24 (92%)]	RR 1.00[49] (0.85-1.17)	nd	
		6 mo (6 mo)							21 (81%) [20 (77%)]	RR 1.05[50] (0.79-1.39)	nd	
Relapse												
Relapse	Eguchi 2010[23] Japan	2 wk (6 mo)	CsA + prednisolone	Prednisolone	26 (26)	26 (26)	S_{Cr} 0.9 mg/dl	6.7 g/d	0 (0%) [0 (0%)]	--	nd	Fair
		4 wk (6 mo)							0 (0%) [1 (4%)]	--	nd	
		3 mo (6 mo)							2 (8%) [2 (8%)]	RR 1.00[51] (0.15-6.57)	nd	
		6 mo (6 mo)							5 (19%) [6 (23%)]	RR 0.83[52] (0.29-2.39)	nd	

[47] Calculated by ERT
[48] Calculated by ERT
[49] Calculated by ERT
[50] Calculated by ERT
[51] Calculated by ERT
[52] Calculated by ERT

Supplementary table 21. Summary table of RCT examining CsA vs. steroid treatment after first relapse in adults with minimal change disease (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
ΔProteinuria	Eguchi 2010[23] Japan	2 wk (6 mo)	CsA + prednisolone	Prednisolone	26 (26)	26 (26)	S_{Cr} 0.9 mg/dl	6.7 g/d	g/d	6.4 (6.9)	-5.9 (-5.1)	<0.05	Fair
		4 wk (6 mo)									-6.4 (-6.5)	NS (0.1)	
		3 mo (6 mo)									-6.2 (-6.7)	NS (0.9)	
		6 mo (6 mo)									-5.8 (-6.4)	NS (0.7)	

Supplementary table 22. Evidence profile of RCTs examining alkylating agents plus steroid treatment vs. control in patients with membranous nephropathy

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	2 RCT (High) 1 SR (4 trials)	174 (89) 196 (103)	Some limitations (-1) No limitations (0)	No important consistencies (0)	Direct (0)	Imprecision (-1)	Low	Insufficient evidence	Critical
ESRD	2 RCT (High) 1 SR (4 trials)	174 (89) 196 (103)	Some limitations (-1) No limitations (0)	No important consistencies (0)	Direct (0)	Imprecision (-1)	Low	Benefit for alkylating agents plus steroids	Critical
Remission	2 RCT (High) 1 SR (4 trials)	174 (89) 176 (94)	Some limitations (-1) No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	Benefit for alkylating agents plus steroids	High
Relapse	2 RCT (High)	174 (89)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	Benefit for alkylating agents plus steroids	High
Proteinuria (categorical)	1 RCT (High)	81 (42)	Some limitations (-1)	NA	Direct (0)	Sparse (-1)	Low	Harm for alkylating agents plus steroids	High
Kidney function (categorical)	1 RCT (High)	81 (42)	Some limitations (-1)	NA	Direct (0)	Sparse (-1)	Low	Possible benefit for alkylating agents plus steroids	High
ΔProteinuria (continuous)	1 RCTs (High)	93 (47)	Some limitations (-1)	NA	Direct (0)	Sparse (-1)	Low	Possible benefit for alkylating agents plus steroids	Moderate
∆Kidney function (continuous)	1 RCTs (High)	93 (47)	Some limitations (-1)	NA	Direct (0)	Sparse (-1)	Low	No difference	Moderate
Adverse events	2 RCTs 1 SR (4 trials)	174 (89) 196 (103)						Higher incidence of patient discontinuation due to adverse events for alkylating agents plus steroids.	Moderate

Balance of potential benefits and harm:
Benefit of alkylating agents plus steroids

Quality of overall evidence:
Moderate

Supplementary table 23. Existing systematic reviews on alkylating agents vs. control for idiopathic membranous nephropathy in adults with nephrotic syndrome

Study, Year, RefID	Study Eligibility Criteria	Interventions (Studies)	Outcomes	Conclusions	Comments	Yes/No
Schieppati 2004[71] Date Base: Cochrane Renal, Cochrane CENTRAL, MEDLINE, Pre-MEDLINE, EMBASE Search Dates: 1966-2003 N Studies: 18 N Subjects: 1025	Randomized controlled trials and quasi-RCTs comparing any immunosuppressive interventions for the treatment of IMN in adults. *Inclusion criteria* • The selected patients were adult subjects with IMN, aged 16 years or older, with nephrotic syndrome. • The diagnosis of IMN was histologically proven. • The assessment of "nephrotic syndrome" relies on that chosen by the authors in the single studies. It must be said that this definition can be heterogeneous. In trials that included a minority of non-nephrotic subjects, when possible, analyses will be restricted to nephrotic patients only. In absence of an explicit definition of "nephrotic syndrome", the cut-off point of urinary protein excretion above 3.5 g/24 h was used.	The following classes of immunosuppressive treatments were considered: • glucocorticoids (alone) • alkylating agents (alone or in association with glucocorticoids) • calcineurin inhibitors (alone or in association with glucocorticoids) • anti-proliferative agents (alone) Control groups were given placebo or no treatment in addition to supportive therapy.	*Definite endpoints* • death • ESRF which requires the initiation of dialysis or kidney transplantation. *Surrogate endpoints* • "Partial remission" • "Complete remission" • "Final proteinuria", measured as g/24 h • "Final serum creatinine", measured as µmol/L • "Final GFR", measured as ml/min/1.73 m^2. The following outcome measures for safety were evaluated: *Side effects* • Proportion of patients experiencing any side effect leading to patient withdrawal. Side effects might include, but are not limited to, leukopaenia, cushingoid features, gastric disorders.	This review failed to show any long-term effect of immunosuppressive treatment on patient and/or renal survival. There was an increased number of discontinuations due to adverse events in immunosuppressive treatment groups. Within the class of alkylating agents there is weak evidence supporting the efficacy of cyclophosphamide as compared to chlorambucil. On the other hand, cyclophosphamide had fewer side effects leading to patient withdrawal than chlorambucil.	Is eligibility criteria similar to the guideline Are there any limitations to systematic review methodology Is limitation to evidence clearly addressed by the authors	Yes No No
Description of limitations of evidence by authors						

Author, Year, RefID	Intervention	Control	Outcome	N studies (N intervention group/ total N)	Pooled RR[1](95% CI)	*P*-value	Test for heterogeneity	
							I^2 Statistic	*P*-value
Schieppati 2004[71]	Alkylating agents	Placebo	Death	4 (103/196)	0.94 (0.14-6.22)	1	0.0%	0.33
Study Years : 1966-2003	Alkylating agents	Placebo	ESRD	4 (103/196)	0.44 (0.11-1.80)	0.30	0.0%	0.44
	Alkylating agents	Placebo	ESRD or Death	4 (103/96)	0.56 (0.18-1.70)	0.30	0.0%	0.40
	Alkylating agents	Placebo	Final proteinuria	4 (103/196)	-2.36 (-4.27, -0.46)	0.02	35.8%	0.21
	Alkylating agents	Placebo	Partial remission	4 (94/176)	1.22	0.60	50.1%	0.11
	Alkylating agents	Placebo	Complete remission	4 (94/176)	2.37 (1.32-4.25)	0.004	0.0%	0.37
	Alkylating agents	Placebo	Complete or partial remission	4 (94/176)	1.55 (0.72-3.34)	0.30	79.9%	0.002
	Alkylating agents	Placebo	Final S_{Cr}	2 (55/107)	-38.37 (-117.67, 100.93)	0.60	87.4%	0.005

Author, Year, RefID	Intervention	Control	Outcome	N studies (N intervention group/ total N)	Pooled RR[1](95% CI)	*P*-value	Test for heterogeneity	
							I^2 Statistic	*P*-value
	Alkylating agents	Placebo	Final GFR	1 (11/22)	1.00 (-18.86, 20.86)	0.90	N/A	N/A
	Alkylating agents	Placebo	D/C due to AEs	4 (103/196)	5.97 (1.08-32.86)	0.04	0.0%	0.90

Supplementary table 24. Summary table of RCTs examining alkylating agents plus steroid treatment vs. control in patients with membranous nephropathy (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
Mortality												
Death	Jha 2007[42] India	10 y (6 mo)	Alternate-month steroid and Cyc	Supportive therapy with dietary sodium restriction, diuretics and anti-HTN agents	47 (51)	46 (53)	S_{Cr} 1.21 mg/dl GFR 89 ml/min	6.11 g/d	1 (2%) [3 (7%)]	RR 0.33 (0.04-3.02) [aaa]	nd	Good
Death	Ponticelli 1995[63] Italy	10 y (6 mo)	Methylprednisolone and chlorambucil	Symptomatic therapy with dietary sodium restriction, diuretics and anti-HTN agents	42 (42)	39 (39)	S_{Cr} 93.8 µmol/L	UPE 6.18 g/d	1 (2%) [3 (8%)]	RR 0.31 (0.03-2.85) [bbb]	nd	Fair
RRT												
10y dialysis-free survival	Jha 2007[42] India	10 y (6 mo)	Alternate-month steroid and Cyc	Supportive therapy with dietary sodium restriction, diuretics and anti-HTN agents	47 (51)	46 (53)	S_{Cr} 1.21 mg/dl GFR 89 ml/min	6.11 g/d	89% [65%]	--	0.016	Good
RRT	Ponticelli 1995[63] Italy	10 y (6 mo)	Methylprednisolone and chlorambucil	Symptomatic therapy with dietary sodium restriction, diuretics and anti-HTN agents	42 (42)	39 (39)	S_{Cr} 93.8 µmol/L	UPE 6.18 g/d	2 (5%) [9 (23%)]	RR 0.21 (0.05-0.90) [ccc]	nd	Fair
Cumulative probability of being alive with functioning kidney at 10 y									0.92 (0.83-1.00) [0.60 (0.42-0.78)]	--	0.0038	Fair
Remission												
Complete remission	Jha 2007[42] India	10 y (6 mo)	Alternate-month steroid and cyclophosphamide	Supportive therapy with dietary sodium restriction, diuretics and anti-HTN agents	47 (51)	46 (53)	S_{Cr} 1.21 mg/dl GFR 89 ml/min	6.11 g/d	15 (32%) [5 (11%)]	RR 2.94 (1.16-7.42) [ddd]	<0.0001	Good
Partial remission									19 (40%) [11 (24%)]	RR 1.69 (0.91-3.15) [eee]	<0.0001	Good

[aaa] Calculated by ERT
[bbb] Calculated by ERT
[ccc] Calculated by ERT
[ddd] Calculated by ERT
[eee] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
Complete or partial remission	Ponticelli 1995[63] Italy	10 y (6 mo)	Methylprednisolone and chlorambucil	Symptomatic therapy with dietary sodium restriction, diuretics and anti-HTN agents	42 (42)	39 (39)	S_{Cr} 93.8 µmol/L	UPE 6.18 g/d	35 (83%) [15 (38%)]	RR 2.17 (1.42-3.30) [fff]	nd	Fair
Complete remission									17 (40%) [2 (5%)]	RR 7.89 (1.95-31.97) [ggg]	nd	Fair
Partial remission									9 (21%) [11 (28%)]	RR 0.76 (0.35-1.63) [hhh]	nd	Fair
Relapse												
Relapse	Jha 2007[42] India	10 y (6 mo)	Alternate-month steroid and Cyc	Supportive therapy with dietary sodium restriction, diuretics and anti-HTN agents	47 (51)	46 (53)	S_{Cr} 1.21 mg/dl GFR 89 ml/min	6.11 g/d	4 of 34 (12%) [8 of 16 (9%)]	RR 0.24 (0.08-0.67) [iii]	nd	Good
Relapse	Ponticelli 1995[63] Italy	10 y (6 mo)	Methylprednisolone and chlorambucil	Symptomatic therapy	42 (42)	39 (39)	S_{Cr} 93.8 µmol/L	UPE 6.18 g/d	4 of 35 (10%) [nd]	--	nd	Poor
Proteinuria												
Patients with nephrotic syndrome at last follow-up	Ponticelli 1995[63] Italy	10 y (6 mo)	Methlyprednisolone and chlorambucil	Supportive therapy of low salt diet, diuretics and anti-HTN medication	42 (42)	39 (39)	S_{Cr} 93.8 µmol/L	UPE 6.18 g/d	9 (21%) [6 (15%)]	RR 0.46 (0.15-1.42) [jjj]	nd	Fair
Kidney function												
↑S_{Cr} ≥50%	Ponticelli 1995[63] Italy	10 y (6 mo)	Methlyprednisolone and chlorambucil	Supportive therapy of low salt diet, diuretics and anti-HTN medication	42 (42)	39 (39)	S_{Cr} 93.8 µmol/L	UPE 6.18 g/d	4 (10%) [8 (21%)]	RR 1.39 (0.55-3.55) [kkk]	nd	Fair
Adverse Events												
AE-infections	Jha 2007[42] India	10 y (6 mo)	Alternate-month steroid and Cyc	Supportive therapy with dietary sodium restriction,	47 (51)	46 (53)	S_{Cr} 1.21 mg/dl GFR 89 ml/min	6.11 g/d	7 (15%) [11 (24%)]	RR 0.62 (0.26-1.47) [lll]	NS (0.35)	Good
AE-thrombotic episodes									3 (6%) [4 (8%)]	RR 0.73 (0.17-3.10) [mmm]	nd	Good

[fff] Calculated by ERT
[ggg] Calculated by ERT
[hhh] Calculated by ERT
[iii] Calculated by ERT
[jjj] Calculated by ERT
[kkk] Calculated by ERT
[lll] Calculated by ERT
[mmm] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
AE-malignancy				diuretics and anti-HTN agents					0 (0%) [0 (0%)]	--	nd	Good
D/C due to AE in treatment group	Ponticelli 1995[63] Italy	10 y (6 mo)	Methlyprednisolone and chlorambucil	Supportive therapy of low salt diet, diuretics and anti-HTN medication	42 (42)	39 (39)	S_{Cr} 93.8 μmol/L	UPE 6.18 g/d	4 (10%) [nd]	--	nd	Poor
AE-moderate leukopenia									2 (5%) [nd]	--	nd	Poor
AE-tremors									2 (5%) [nd]	--	nd	Poor
AE-cramps									2 (5%) [nd]	--	nd	Poor
AE-anxiety									2 (2%) [nd]	--	nd	Poor

Supplementary table 25. Summary table of RCTs examining alkylating agents plus steroid treatment vs. control in patients with membranous nephropathy (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
Proteinuria[nnn]	Jha 2007[42] India	10 y (6 mo)	Alternate-month steroid and Cyc	Supportive therapy with dietary sodium restriction, diuretics and anti-HTN agents	47 (51)	46 (53)	S_{Cr} 1.21 mg/dl GFR 89 ml/min	6.11 g/d	g/d	6.11 (5.91)	-5.21 (-3.31)	nd	Fair
S_{Cr}/GFR/CrCl													
MDRD eGFR[ooo]	Jha 2007[42] India	10 y (6 mo)	Alternate-month steroid and Cyc	Supportive therapy with dietary sodium restriction, diuretics and anti-HTN agents	47 (51)	46 (53)	S_{Cr} 1.21 mg/dl GFR 89 ml/min	6.11 g/d	ml/min	89 (84)	-27 (-32)	nd	Fair

[nnn] Estimated from graph
[ooo] Estimated from graph

Supplementary table 26. Summary table of RCTs examining alkylating agents plus steroid treatment vs. ACTH in patients with membranous nephropathy (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
Remission												
Remission	Ponticelli 2006[64] Italy	12 mo (6 mo)	Methlyprednisolone and chlorambucil or Cyc	Tetracosactide (ACTH)	16 (16)	16 (16)	S_{Cr} 0.9 mg/dl	5.5 g/d	15 (93%) [14 (87%)]	RR 1.07 (0.86-1.34)[68]	NS	Poor
Complete remission									5 (31%) [10 (63%)]	RR 0.50 (0.22-1.14)[69]	NS	Poor
Partial remission									10 (63%) [4 (25%)]	RR 2.50 (0.99-6.33)[70]	NS	Poor
Adverse Events												
AE-leukopenia	Ponticelli 2006[64] Italy	12 mo (6 mo)	Methlyprednisolone and chlorambucil or Cyc	Tetracosactide (ACTH)	16 (16)	16 (16)	S_{Cr} 0.9 mg/dl	5.5 g/d	1 (6%) [0 (0%)]	--	nd	Poor
AE-dizziness									0 (0%) [1 (6%)]	--	nd	Poor
AE-glucose intolerance									2 (13%) [2 (13%)]	--	nd	Poor
AE-diarrhea									0 (0%) [1 (6%)]	--	nd	Poor
AE-onycodystrophy									0 (0%) [1 (6%)]	--	nd	Poor
AE-folliculitis									0 (0%) [1 (6%)]	--	nd	Poor
AE-bronzing of skin									0 (0%) [1 (6%)]	--	nd	Poor

[68] Calculated by ERT
[69] Calculated by ERT
[70] Calculated by ERT

Supplementary table 27. Summary table of RCTs examining alkylating agents plus steroid treatment vs. ACTH in patients with membranous nephropathy (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
Median	Ponticelli 2006[64] Italy	12 mo (6 mo)	Methlyprednisolone	Tetracosactide (ACTH)	16 (16)	16 (16)	S_{Cr} 0.9 mg/dl	5.5 g/d	g/d	5.1 (6.0)	-3.0 (-5.7)	NS	Poor
S_{Cr}/GFR/CrCl													
Median S_{Cr}	Ponticelli 2006[64] Italy	12 mo (6 mo)	Methlyprednisolone	Tetracosactide (ACTH)	16 (16)	16 (16)	S_{Cr} 0.9 mg/dl	5.5 g/d	mg/dl	0.9 (0.9)	+0.1 (+0.1)	NS	Poor

Supplementary table 28. Evidence profile of RCTs examining CsA/TAC treatment vs. control for idiopathic membranous nephropathy

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	1 SR (3 RCTs)	104 (63)	Some limitation (-1)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Low	Insufficient evidence	Critical
ESRD	1 SR (3 RCTs)	104 (63)	Some limitation (-1)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Low	Insufficient evidence	Critical
Remission	1 RCT (High) 1 SR (2 RCTs)	48 (25) 104 (63)	No limitations (0) Some limitation (-1)	Important inconsistencies (-1)	Direct (0)	None (0)	Low	Benefit for tacrolimus in one RCT. No difference for cyclosporine.	High
Relapse	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Kidney function (categorical)	1 RCT (High)	48 (25)	No limitations (0)	N/A	Direct (0)	Sparse (-1)	Moderate	Benefit for tacrolimus	High
ΔProteinuria (continuous)	1 RCT (High)	48 (25)	No limitations (0)	No important inconsistencies (0)	Direct (0)	Sparse (-1)	Moderate	Benefit for tacrolimus.	Moderate
∆Kidney function (continuous)	0 RCTs	--	--	--	--	--	--	--	Moderate
Adverse events	1 RCT 1 SR (3 RCTs)	48 (25) 104 (63)						Possible increase in glucose intolerance with tacrolimus.	Moderate

Balance of potential benefits and harm:
Benefit for tacrolimus. No difference for cyclosporine.

Quality of overall evidence:
Low

Supplementary table 29. Existing systematic reviews on CsA/TAC treatment vs. placebo for idiopathic membranous nephropathy in adults with nephrotic syndrome

Study, Year, RefID	Study Eligibility Criteria	Interventions (Studies)	Outcomes	Conclusions	Comments	Yes/No
Schieppati 2004[71]	Randomized controlled trials and quasi-RCTs comparing any immunosuppressive interventions for the treatment of IMN in adults. *Inclusion criteria* • The selected patients were adult subjects with IMN, aged 16 years or older, with nephrotic syndrome. • The diagnosis of IMN was histologically proven. • The assessment of "nephrotic syndrome" relies on that chosen by the authors in the single studies. It must be said that this definition can be heterogeneous. In trials that included a minority of non-nephrotic subjects, when possible, analyses will be restricted to nephrotic patients only. In absence of an explicit definition of "nephrotic syndrome", the cut-off point of urinary protein excretion above 3.5 g/24 h was used.	The following classes of immunosuppressive treatments were considered: • glucocorticoids (alone) • alkylating agents (alone or in association with glucocorticoids) • calcineurin inhibitors (alone or in association with glucocorticoids) • anti-proliferative agents (alone) Control groups were given placebo or no treatment in addition to supportive therapy.	*Definite endpoints* • death • ESRF which requires the initiation of dialysis or kidney transplantation. *Surrogate endpoints* • "Partial remission" • "Complete remission" • "Final proteinuria", measured as g/24 h • "Final serum creatinine", measured as µmol/L • "Final GFR", measured as ml/min/1.73 m^2. The following outcome measures for safety were evaluated: *Side effects* • Proportion of patients experiencing any side effect leading to patient withdrawal. Side effects might include, but are not limited to, leukopaenia, cushingoid features, gastric disorders.	This review failed to show any long-term effect of immunosuppressive treatment on patient and/or renal survival. There was an increased number of discontinuations due to adverse events in immunosuppressive treatment groups. Within the class of alkylating agents there is weak evidence supporting the efficacy of cyclophosphamide as compared to chlorambucil. On the other hand, cyclophosphamide had fewer side effects leading to patient withdrawal than chlorambucil.	Is eligibility criteria similar to the guideline	Yes
Date Base: Cochrane Renal, Cochrane CENTRAL, MEDLINE, Pre-MEDLINE, EMBASE						
Search Dates: 1966-2003					Are there any limitations to systematic review methodology	No
N Studies: 18						
N Subjects: 1025					Is limitation to evidence clearly addressed by the authors	No
Description of limitations of evidence by authors						

Author, Year, RefID	Intervention	Control	Outcome	N studies (N intervention group/ total N)	Pooled RR[71] (95% CI)	*P*-value	Test for heterogeneity	
							I^2 Statistic	*P*-value
Schieppati 2004[71]	CsA	Placebo	Death	3 (63/104)	2.70 (0.13-58.24)	0.50	N/A	N/A
Study Years : 1966-2003	CsA	Placebo	ESRD	3 (63/104)	0.88 (0.21-3.66)	0.90	42%	0.18
Declining renal function at baseline: No: 1 study Yes: 2 studies	CsA	Placebo	ESRD or Death	3 (63/104)	0.93 (0.32-2.71)	0.90	20%	0.29
Use of ACE-I during follow-up: Yes, confounding effect: 2 studies No confounding effect: 1 study	CsA	Placebo	Final proteinuria	2 (19/38)	WMD[72] -0.08 (-9.29, 9.13)	1	87%	0.005
Mean follow-up: 12, 15, and 21 mo	CsA	Placebo	Partial remission	2 (54/87)	1.08 (0.76-1.55)	0.70	0%	0.60
Grading: 2 A and 1 B	CsA	Placebo	Complete remission	2 (54/87)	1.10 (0.41-2.96)	0.80	0%	0.46
	CsA	Placebo	Complete or partial remission	2 (54/87)	1.00 (0.72-1.40)	1	0%	0.39

[71] RR is equal to Intervention/Control

[72] Weighted Mean Difference is equal to Intervention minus Control

CsA	Placebo	Final S_{Cr}	1 (10/21)	WMD 11.50 (-50.19, 73.19)	0.70	N/A	N/A
CsA	Placebo	Final GFR	2 (19/38)	WMD 8.31 (-10.83, 27.45)	0.40	35%	0.21
CsA	Placebo	D/C due to AEs	3 (63/104)	5.45 (0.29-101.55)	0.30	N/A	N/A

Supplementary table 30. Summary table of RCT examining CsA/TAC treatment vs. control for idiopathic membranous nephropathy (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
Remission (PR or CR)												
2 mo	Praga 2007[69] Spain	2 mo (18 mo)	Tac	Control	25 (25)	23 (23)	S_{Cr} 0.98 mg/dl GFR 104 ml/min	7.2 g/d	9 (36%) [2 (9%)]	RR 4.14 (1.00-17.19) [73]	<0.04	Good
6 mo		6 mo (18 mo)							14 (56%) [3 (13%)]	RR 4.29 (1.41-13.04) [74]	<0.01	Good
12 mo		12 mo (18 mo)							18 (72%) [5 (22%)]	RR 3.31 (1.47-7.47) [75]	<0.001	Good
18 mo		18 mo (18 mo)							19 (76%) [6 (30%)]	RR 2.91 (1.41-6.00) [76]	0.003	Good
Probability of PR or CR												
6 mo	Praga 2007[69] Spain	6 mo (18 mo)	Tac	Control	25 (25)	23 (23)	S_{Cr} 0.98 mg/dl GFR 104 ml/min	7.2 g/d	58% [10%]	--	<0.00001	Good
12 mo		12 mo (18 mo)							82% [24%]	--		Good
18 mo		18 mo (18 mo)							94% [35%]	--		Good
Mean time to PR or CR												
Mean time (mo)	Praga 2007[69] Spain	18 mo (18 mo)	Tac	Control	25 (25)	23 (23)	S_{Cr} 0.98 mg/dl GFR 104 ml/min	7.2 g/d	6.1 [11.3]	--	0.003	Good
Kidney function												
↑S_{Cr} 50%	Praga 2007[69] Spain	18 mo (18 mo)	Tac	Control	25 (25)	23 (23)	S_{Cr} 0.98 mg/dl GFR 104 ml/min	7.2 g/d	1 (4%) [6 (26%)]	RR 0.15 (0.02-1.18) [77]	0.03	Good
Adverse Events												
AE-glucose intolerance	Praga 2007[69] Spain	18 mo (18 mo)	Tac	Control	25 (25)	23 (23)	S_{Cr} 0.98 mg/dl GFR 104 ml/min	7.2 g/d	4 (16%) [2 (9%)]	RR 1.84 (0.37-9.12) [78]	nd	Good
AE-chest pain									0 (0%) [2 (9%)]	--	nd	Good
AE-diarrhea									2 (8%) [0 (0%)]	--	nd	Good
AE- gouty arthritis									1 (4%) [0 (0%)]	--	nd	Good
AE- UTI									0 (0%) [1 (4%)]	--	nd	Good

[73] Calculated by ERT
[74] Calculated by ERT
[75] Calculated by ERT
[76] Calculated by ERT
[77] Calculated by ERT
[78] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
AE- nausea									1 (4%) [0 (0%)]	--	nd	Good
AE- headache									1 (4%) [0 (0%)]	--	nd	Good
AE-tremor									1 (4%) [0 (0%)]	--	nd	Good

Supplementary table 31. Summary table of RCT examining CsA/TAC treatment vs. control for idiopathic membranous nephropathy (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
12 mo	Praga 2007[69] Spain	12 mo (18 mo)	Tac	Control	25 (25)	23 (23)	S_{Cr} 0.98 mg/dl GFR 104 ml/min	7.2 g/d	g/d	7.2 (8.4)	-5.6 (-4.3)	0.045	Fair
18 mo										7.2 (8.4)	-5.3 (-5.2)	0.048	Fair

Supplementary table 32. Evidence profile of RCTs examining MMF treatment vs. control for idiopathic membranous nephropathy in adults with nephrotic syndrome

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	0 RCTs	--	--	--	--	--	--	--	Critical
ESRD	0 RCTs	--	--	--	--	--	--	--	Critical
Remission	3 RCTs (High)	73 (37)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Insufficient evidence	High
Relapse	2 RCT (High)	41 (22)	Some limitations (-1)	Important inconsistencies (-1)	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Insufficient evidence	High
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Kidney function (categorical)	2 RCT (High)	52 (26)	Some limitations (-1)	Important inconsistencies (-1)	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Insufficient evidence	High
ΔProteinuria (continuous)	3 RCTs (High)	73 (37)	Some limitations (-1)	Important inconsistencies (0)	Direct (0)	Sparse (-1)	Low	No difference	Moderate
∆Kidney function (continuous)	2 RCT (High)	41 (22)	Some limitations (-1)	No important inconsistencies (-1)	Direct (0)	Sparse (-1)	Low	No difference	Moderate
Adverse events	2 RCT	52 (26)						Higher incidence of adverse events and serious adverse events with MMF	Moderate

Balance of potential benefits and harm:
Insufficient evidence

Quality of overall evidence:
Very low

Supplementary table 33. Summary table of RCTs examining MMF treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
Remission												
Complete remission	Dussol 2008[22] France	6 mo (12 mo)	MMF and conservative treatment	Conservative treatment with ACE-I, statins, low-salt and low-protein diet, and loop diuretic	15 (19)	17 (17)	S_{Cr} 1.01 mg/dl GFR 92 ml/min	6.2 g/d	1 (6%) [0 (0%)]	RR 1.25 (0.65-2.40)	NS (0.3)	Fair
Partial remission									4 (27%) [3 (18%)]		NS (0.8)	Fair
Complete remission		12 mo (12 mo)	MMF and conservative treatment	Conservative treatment with ACE-I, statins, low-salt and low-protein diet, and loop diuretic	15 (19)	17 (17)	S_{Cr} 1.01 mg/dl GFR 92 ml/min	6.2 g/d	1 (6%) [2 (12%)]	RR 0.92 (0.48-1.75)	NS (0.5)	Fair
Partial remission									6 (40%) [5 (29%))		NS (0.9)	Fair
Remissions									37% [41%]	--	nd	Fair
Complete remission	Chan 2007[11] China	15 mo (6 mo)	MMF and prednisone	Modified Ponticelli regimen	11 (11)	9 (9)	100 µmol/L	5.7 g/d	3 (27%) [3 (33%)]	RR 0.82 (0.22-3.11) [79]	NS	Fair
Partial remission									4 (36%) [3 (33%)]	RR 1.09 (0.33-3.66) [80]	NS	Fair
Composite endpoint of CR or PR									64% [68%]	--	NS	Fair
Time to remission (mo)									5 [6]	--	NS	Fair
Complete remission	Nayagam 2008[59] India	12 mo (6 mo)	MMF and prednisone	Conventional therapy with methlyprednisolone and p.o. prednisone	11 (11)	10 (10)	GFR 86 ml/min	UPCR 4.68 mg/mg (MN and FSGS)	5 (45%) [3 (30%)]	RR 1.52 (0.48-4.77) [81]	nd	Good
Partial remission									2 (18%) [5 (50%)]	RR 0.36 (0.09-1.47) [82]	nd	Good
Time to remission (wk)									9.2 [10.4]	--	nd	Good
Relapse or Failure												
Treatment failure	Chan 2007[11] China	15 mo (6 mo)	MMF and prednisone	Modified Ponticelli regimen	11 (11)	9 (9)	100 µmol/L	5.7 g/d	4 (36%) [3 (33%)]	RR 1.09 (0.33-3.66) [83]	NS	Fair
Relapse									2 (18%) [1 (11%)]	RR 2.27 (0.23-22.56) [84]	NS	Fair
Relapse in CR or PR (n=13)									3 (23%)	--	nd	Fair
Relapse	Nayagam 2008[59] India	12 mo (6 mo)	MMF and prednisone	Conventional therapy with	11 (11)	10 (10)	GFR 86 ml/min	UPCR 4.68 mg/mg	0 (0%) [1 (10%)]	--	nd	Good

[79] Calculated by ERT
[80] Calculated by ERT
[81] Calculated by ERT
[82] Calculated by ERT
[83] Calculated by ERT
[84] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
				methlyprednisolone and p.o. prednisone				(MN and FSGS)				
Kidney Function												
↑S_{Cr} 20%	Dussol 2008[22] France	12 mo (12 mo)	MMF and conservative treatment	Conservative treatment with ACE-I, statins, low-salt and low-protein diet, and loop diuretic	15 (19)	17 (17)	S_{Cr} 1.01 mg/dl GFR 92 ml/min	6.2 g/d	0 (0%) [0 (0%)]	--	nd	Fair
≥15% ↑S_{Cr}	Chan 2007[11] China	15 mo (6 mo)	MMF and prednisone	Modified Ponticelli regimen	11 (11)	9 (9)	100 µmol/L	5.7 g/d	2 (18%) [0 (0%)]	--	nd	Poor
≥15% ↓S_{Cr}									3 (27%) [1 (11%)]	2.45 (0.31-19.74) [85]	nd	Poor
Adverse Events												
Serious AEs	Dussol 2008[22] France	12 mo (12 mo)	MMF and conservative treatment	Conservative treatment with ACE-I, statins, low-salt and low-protein diet, and loop diuretic	15 (19)	17 (17)	S_{Cr} 1.01 mg/dl GFR 92 ml/min	6.2 g/d	3 (20%) [0 (0%)]	--	nd	Fair
AE-muscular pain									4 (27%) [5 (29%)]	RR 0.91 (0.30-2.71) [86]	nd	Fair
AE-anemia									2 (13%) [1 (6%)]	RR 2.27 (0.23-22.56) [87]	nd	Fair
AE-nausea/vomiting									2 (13%) [1 (6%)]	RR 2.27 (0.23-22.56) [88]	nd	Fair
AE-hypotension									1 (7%) [1 (6%)]	RR 1.13 (0.08-16.59) [89]	nd	Fair
AE-cough									1 (7%) [2 (12%)]	RR 0.57 (0.06-5.64) [90]	nd	Fair
AE-acute bronchitis									0 (0%) [1 (6%)]	--	nd	Fair
AE-cytolysis									1 (7%) [0 (0%)]	--	nd	Fair
AE-infection	Chan 2007[11] China	15 mo (6 mo)	MMF and prednisone	Modified Ponticelli regimen	11 (11)	9 (9)	100 µmol/L	5.7 g/d	3 (27%) [2 (22%)]	RR 1.23 (0.26-5.82) [91]	nd	Poor
AE-leucopenia									6 (30%)	--	nd	Poor
AE-new onset DM									1 (9%) [1 (11%)]	RR 0.82 (0.06-11.33) [92]	nd	Poor

[85] Calculated by ERT
[86] Calculated by ERT
[87] Calculated by ERT
[88] Calculated by ERT
[89] Calculated by ERT
[90] Calculated by ERT
[91] Calculated by ERT
[92] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
AE-death									0 (0%) [0 (0%)]	--	nd	Poor

Supplementary table 34. Summary table of RCTs examining MMF treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Units	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
Mean UPCR	Dussol 2008[22] France	12 mo (12 mo)	MMF and conservative treatment	Conservative treatment with ACE-I, statins, low-salt and low-protein diet, and loop diuretic	15 (19)	17 (17)	S_{Cr} 1.01 mg/dl GFR 92 ml/min	6.2 g/d	nd	4865 (6548)	+213.07 (-1834.6)	0.3	Fair
Proteinuria	Chan 2007[11] China	15 mo (6 mo)	MMF and prednisone	Modified Ponticelli regimen	11 (11)	9 (9)	100 µmol/L	5.7 g/d	g/d	5.3 (6.6)	-3.8 (-6.2)	nd	Poor
ΔUPCR	Nayagam 2008[59] India	12 mo (6 mo)	MMF and prednisone	Conventional therapy with methlyprednisolone and p.o. prednisone	11 (11)	10 (10)	GFR 86 ml/min	UPCR 4.68 mg/mg (MN and FSGS)	mg/mg	5.3 (5.1)	-4.6 (-4.0)	nd	Fair
S_{Cr}/GFR/CrCl													
S_{Cr}	Chan 2007[11] China	15 mo (6 mo)	MMF and prednisone	Modified Ponticelli regimen	11 (11)	9 (9)	100 µmol/L	5.7 g/d	µmol/L	100.1 (95.4)	20.3 (-5.8)	nd	Poor
CrCl									ml/min	71.5 (91.3)	5.0 (5.9)	nd	Poor
MDRD GFR	Nayagam 2008[59] India	12 mo (6 mo)	MMF and prednisone	Conventional therapy with methlyprednisolone and p.o. prednisone	11 (11)	10 (10)	GFR 86 ml/min	UPCR 4.68 mg/mg	ml/min	85 (80)	-4 (-4)	nd	Good

Supplementary table 35. Evidence profile of RCTs examining alternate-day prednisone treatment vs. control in adults and children with MPGN

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	1 RCT (High)	77 (44)	Serious limitations (-2)	N/A	Direct (0)	Sparse (-1)	Very low	No difference	Critical
ESRD	1 RCT (High)	18 (8)	Some limitations (-1)	N/A	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Benefit with prednisone	Critical
Remission	1 RCT (High)	18 (8)	Some limitations (-1)	N/A	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Insufficient evidence	High
Relapse	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Kidney function (categorical)	2 RCTs (High)	95 (52)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	Sparse (-1)	Low	Possible benefit with prednisone in Type I and III	High
ΔProteinuria (continuous)	1 RCT (High)	18 (8)	Serious limitations (-2)	N/A	Direct (0)	Sparse (-1)	Very low	Possible benefit with prednisone	Moderate
ΔKidney function (continuous)	1 RCT (High)	18 (8)	Serious limitations (-2)	N/A	Direct (0)	Sparse (-1)	Very low	Benefit with prednisone	Moderate
Adverse events	1 RCT (High)	77 (44)						Higher incidence of hypertensive encephalopathy and steroid toxicity with prednisone.	Moderate

Balance of potential benefits and harm:
Potential benefit for prednisone

Quality of overall evidence:
Very low

Supplementary table 36. Summary table of RCTs examining alternate-day prednisone treatment vs. control in patients with MPGN (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
Mortality												
Death	Tarshish 1992[81] US, Europe, Mexico	63 mo (41 mo)	Alternate-day prednisone	Placebo	44 (47)	33 (33)	GFR 112 ml/min/1.73 m^2 (62 µmol/L)	122 mg/h/m^2	2 (5%) [4 (12%)]	RR 0.38 (0.07-1.93) [93]	0.240	Poor
ESRD												
ESRD	Mota-Hernandez 1985[58] Mexico	2-5 y (nd)	Alternate-day prednisone	Lactose	8 (8)	10 (10)	S_{Cr} 0.78 mg/dl	99 mg/h/m^2	0 (0%) [4 (40%])	--	nd	Fair
Remission												
1, 2, or 8 y	Mota-Hernandez 1985[58] Mexico	Up to 8 y (nd)	Alternate-day prednisone	Lactose	8 (8)	10 (10)	S_{Cr} 0.78 mg/dl	99 mg/h/m^2	1 (13%) [2 (20%)]	RR 0.63 (0.07-5.72) [94]	0.677	Fair
Kidney Function												
"Moderate" increase in S_{Cr}	Mota-Hernandez 1985[58] Mexico	5 y (nd)	Alternate-day prednisone	Lactose	8 (8)	10 (10)	S_{Cr} 0.78 mg/dl	99 mg/h/m^2	3 (38%) [0 (0%)]	--	nd	Poor
↑S_{Cr} ≥30% or ≥0.4 mg/dl (35 µmol/L)	Tarshish 1992[81] US, Europe, Mexico	63 mo (41 mo)	Alternate-day prednisone	Placebo	44 (47)	33 (33)	GFR 112 ml/min/1.73 m^2 (62 µmol/L)	122 mg/h/m^2	16 (36%) [18 (55%)]	RR 0.67 (0.40-1.10) [95]	0.112	Fair
		130 mo (survival analysis)							59% [88%]	--	0.07	
		63 mo (41 mo)			Type I, III 31 (33)	26 (26)			9 (29%) [15 (58%)]	RR 0.45 (0.23-0.90) [96]	0.035	
					Type II 9 (9)	5 (5)			5 (56%) [3 (60%)]	RR 0.93 (0.37-2.33) [97]	0.870	
S_{Cr}≥4.0 mg/dl (350 µmol/L)					44 (47)	33 (33)			13 (30%) [14 (42%)]	RR 0.70 (0.38-1.28) [98]	0.241	Fair
Adverse Events												

[93] Calculated by ERT
[94] Calculated by ERT
[95] Calculated by ERT
[96] Calculated by ERT
[97] Calculated by ERT
[98] Calculated by ERT

AE-Hypertensive encephalopathy	Tarshish 1992[81] US, Europe, Mexico	63 mo (41 mo)	Alternate-day prednisone	Placebo	44 (47)	33 (33)	GFR 112 ml/min/1.73 m^2 (62 µmol/L)	122 mg/h/m^2	3 (6%) [2 (6%)]	RR 1.13 (0.20-6.35) [99]	0.894	Fair
AE-Steroid toxicity requiring discontinuation									2 (4%) [0 (0%)]	--	nd	Fair

[99] Calculated by ERT

Supplementary table 37. Summary table of RCTs examining alternate-day prednisone treatment vs. control in patients with MPGN (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
Proteinuria	Mota-Hernandez 1985[58] Mexico	6.5 y (nd)	Alternate-day prednisone	Lactose	8 (8)	10 (10)	S_{Cr} 0.78 mg/dl	99 mg/h/m^2	mg/h/m^2	99 (97)	-3.63 (-0.05)	nd	Poor
S_{Cr}/GFR/CrCl													
S_{Cr}	Mota-Hernandez 1985[58] Mexico	6.5 y (nd)	Alternate-day prednisone	Lactose	8 (8)	10 (10)	S_{Cr} 0.78 mg/dl	99 mg/h/m^2	mg/dl	0.78 (0.82)	-0.50 (+4.09)	nd	Poor

Supplementary table 38. Summary table of studies examining dipyridamole plus aspirin treatment vs. placebo in patients with MPGN (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Time to outcome Intervention [Control]	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
ESRD													
ESRD (dialysis)	Donadio [100] 1984[19] US	≤7 y (12 mo)	Dipyridamole and aspirin	Placebo	21 (25)	19 (25)	GFR 69.5 ml/min/1.73 m^2	5.9 g/d	Mean 62 (range 37-70) mo [33 (10-63)]	3 (14%) [9 (47%)]	RR 0.030 (0.10-0.95) [101]	0.03[102]	Fair
Kidney Function													
↓GFR by ≥25%	Donadio [103] 1984[19] US	12 mo (12 mo)	Dipyridamole and aspirin	Placebo	21 (25)	19 (25)	GFR 69.5 ml/min/1.73 m^2	5.9 g/d	--	3 (14%) [7 (37%)]	RR 0.39 (0.12-1.29) [104]	<0.05	Fair
No. of nephrotic patients	Zauner 1994[92] Germany	12 mo (36 mo)	Dipyridamole aspirin, protein restriction and anti-HTN therapy	Protein restriction and anti-HTN therapy	10 (10)	8 (8)	S_{Cr} 1.79 mg/dl	8.28 g/d	--	30% (100%)	--	nd	Fair
No. of nephrotic patients		36 mo (36 mo)								10% (75%)	--	nd	Fair
Adverse Events													
AE- painful ecchymosis	Donadio [105] 1984[19] US	12 mo (12 mo)	Dipyridamole and aspirin	Placebo	21 (25)	19 (25)	GFR 69.5 ml/min/1.73 m^2	5.9 g/d	--	5% [0%]	--	nd	Fair
AE-recurrent gastric ulcer with bleeding										5% [0%]	--	nd	Fair
AE-rectal bleeding										5% [0%]	--	nd	Fair
AE-acute interstitial nephritis due to furosemide										0% [5%]	--	nd	Fair

[100] Subsequent publication (Donadio JV. 1989 AJKD Dec 14(5): 445) indicated that results are heavily influenced by lead-time bias, so no evidence profile was made.
[101] Calculated by ERT
[102] Calculated by ERT. Odds ratio
[103] Subsequent publication (Donadio JV. 1989 AJKD Dec 14(5): 445) indicated that results are heavily influenced by lead-time bias, so no evidence profile was made.
[104] Calculated by ERT
[105] Subsequent publication (Donadio JV. 1989 AJKD Dec 14(5): 445) indicated that results are heavily influenced by lead-time bias, so no evidence profile was made.

Supplementary table 39. Summary table of studies examining dipyridamole plus aspirin treatment vs. placebo in patients with MPGN (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
12 mo	Zauner 1994[92] Germany	12 mo (36 mo)	Dipyridamole aspirin, protein restriction and anti-HTN therapy	Protein restriction and anti-HTN therapy	10 (10)	8 (8)	S_{Cr} 1.79 mg/dl	8.28 g/d	g/d	8.28 (7.11)	-5.72 (-1.7)	nd	Poor
36 mo									g/d	8.28 (7.11)	-6.67 (-2.77)	nd	Poor
S_{Cr}/GFR/CrCl													
ΔGFR 12 mo	Donadio [106] 1984[19] US	12 mo (12 mo)	Dipyridamole and aspirin	Placebo	18[107] (25)	18 (25)	GFR 69.5 ml/min/1.73 m^2	5.9 g/d	ml/min/1.73 m^2	NA	-1.3 (-19.6)	0.05 <0.02[108]	Poor
ΔS_{Cr} 12 mo									mg/dl	NA	+0.18 (+1.1)	NS	Poor
S_{Cr}	Zauner 1994[92] Germany	36 mo (36 mo)	Dipyridamole aspirin, protein restriction and anti-HTN therapy	Protein restriction and anti-HTN therapy	10 (10)	8 (8)	S_{Cr} 1.79 mg/dl	8.28 g/d	mg/dl	1.79 (1.79)	-0.01 (-0.18)	nd	Poor

[106] Subsequent publication (Donadio JV. 1989 AJKD Dec 14(5): 445) indicated that results are heavily influenced by lead-time bias, so no evidence profile was made.
[107] Restricted to those without treatment complications.
[108] By 2-sample t-test and by rank-sum test, respectively.

Supplementary table 40. Summary table of study examining warfarin plus dipyridamole treatment vs. control in patients with MPGN (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	OR/RR/HR		
ESRD												
ESRD	Zimmerman 1983[93] US	12 mo (12 mo)	Warfarin and dipyridamole	No treatment	8 (11)	10 (11)	S_{Cr} 1.6 mg/dl	2.91 g/d	0 (0%) [2 (20%)]	--	nd	Poor
Kidney function												
↑S_{Cr} >0.2 mg/dl	Zimmerman 1983[93] US	12 mo (12 mo)	Warfarin and dipyridamole	No treatment	8 (11)	10 (11)	S_{Cr} 1.6 mg/dl	2.91 g/d	1 (13%) [6 (60%)]	RR 0.21 (0.03-1.40)	0.06 (X^2)	Poor
↓S_{Cr} >0.2 mg/dl									2 (25%) [0 (0%)]	--	nd	Poor
"Significant" ↓1/ S_{Cr} (P<0.05)									0 (0%) [5 (50%)]	--	<0.03	Poor
Doubling of S_{Cr}									0 (0%) [4 (40%)]	--	nd	Poor

Supplementary table 41. Summary table of study examining warfarin plus dipyridamole treatment vs. control in patients with MPGN (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
Urine protein	Zimmerman 1983[93] US	12 mo (12 mo)	Warfarin and dipyridamole	No treatment	8 (11)	10 (11)	S_{Cr} 1.6 mg/dl	2.91 g/d	g/d	6.2 (6.8)	-3.0 (-0.1)	NS (<0.10)	Poor
S_{Cr}/GFR/CrCl													
S_{Cr}	Zimmerman 1983[93] US	12 mo (12 mo)	Warfarin and dipyridamole	No treatment	8 (11)	10 (11)	S_{Cr} 1.6 mg/dl	2.91 g/d	mg/dl	1.6 (1.6)	-0.2 (+2.0)	<0.01	Poor
1/S_{Cr} slope									dl/mg	--	+0.091 (-0.208)	<0.025	Poor

Supplementary table 42. Summary table of studies examining prednisone or CsA treatment vs. control in patients with schistosoma and nephropathy (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		Results				*P* value	Quality
			Intervention	Control	Intervention	Control	GFR/S_{Cr}	Proteinuria	Events (%) Intervention [Control]	RR/OR/HR		
Remission												
Complete remission	Sobh 1989[74] Netherlands	12 mo (3 d)	Oxamniquine +praziquantel + prednisone	Oxamniquine +praziquantel	10 (10)	8 (8)	S_{Cr} 0.99	4.47 g/d	2 (20%) [0 (0%)]	--	nd	Poor
			Oxamniquine +praziquantel +CsA	Oxamniquine +praziquantel	8 (8)		S_{Cr} 0.68	2.92 g/d	1 (13%) [0 (0%)]	--	nd	Poor
Partial remission			Oxamniquine +praziquantel + prednisone	Oxamniquine +praziquantel	10 (10)		S_{Cr} 0.99	4.47 g/d	3 (30%) [1 (13%)]	RR 2.40 (0.30-18.90)[109]	nd	Poor
			Oxamniquine +praziquantel +CsA	Oxamniquine +praziquantel	8 (8)		S_{Cr} 0.68	2.92 g/d	1 (13%) [1 (13%)]	RR 1.00 (0.07-13.37)[110]	nd	Poor
Kidney Function												
↑S_{Cr}	Sobh 1989[74] Netherlands	12 mo (3 d)	Oxamniquine +praziquantel + prednisone	Oxamniquine +praziquantel	10 (10)	8 (8)	S_{Cr} 0.99	4.47 g/d	0 (0%) [1 (13%)]	--	nd	Poor
			Oxamniquine +praziquantel +CsA	Oxamniquine +praziquantel	8 (8)		S_{Cr} 0.68	2.92 g/d	1 (13%) [1 (13%)]	RR 1.00 (0.07-13.37)[111]	nd	Poor
↓S_{Cr}			Oxamniquine +praziquantel + prednisone	Oxamniquine +praziquantel	10 (10)		S_{Cr} 0.99	4.47 g/d	2 (20%) [0 (0%)]	--	nd	Poor
			Oxamniquine +praziquantel +CsA	Oxamniquine +praziquantel	8 (8)		S_{Cr} 0.68	2.92 g/d	0 (0%) [0 (0%)]	--	nd	Poor
Adverse Events												
Drug toxicity	Sobh 1989[74] Netherlands	12 mo (3 d)	Oxamniquine +praziquantel + prednisone	Oxamniquine +praziquantel	10 (10)	8 (8)	S_{Cr} 0.99	4.47 g/d	2 (20%) [0 (0%)]	--	nd	Poor
			Oxamniquine +praziquantel +CsA	Oxamniquine +praziquantel	8 (8)		S_{Cr} 0.68	2.92 g/d	2 (25%) [0 (0%)]	--	nd	Poor

[109] Calculated by ERT
[110] Calculated by ERT
[111] Calculated by ERT

Supplementary table 43. Summary table of studies examining prednisone or cyclosporine treatment vs. control in patients with schistosoma and nephropathy (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results			*P* value	Quality
			Intervention	Control	Intervention	Control				Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria														
24-h proteinuria	Sobh 1989[74] Netherlands	12 mo (3 d)	Oxamniquine +praziquantel + prednisone	Oxamniquine +praziquantel	10 (10)	8 (8)	S_{Cr} 0.99	4.47 g/d	nd	g/d	4.47 (3.9)	-0.55 (+0.09)	nd	Poor
			Oxamniquine +praziquantel +CsA	Oxamniquine +praziquantel	8 (8)		S_{Cr} 0.68	2.92 g/d			2.92 (3.9)	+0.64 (+0.03)	nd	Poor
S_{Cr}/GFR/CrCl														
S_{Cr}	Sobh 1989[74] Netherlands	12 mo (3 d)	Oxamniquine +praziquantel + prednisone	Oxamniquine +praziquantel	10 (10)	8 (8)	S_{Cr} 0.99	4.47 g/d	nd	nd	0.99 (0.82)	-0.04 (+0.03)	nd	Poor
			Oxamniquine +praziquantel +CsA	Oxamniquine +praziquantel	8 (8)		S_{Cr} 0.68	2.92 g/d			0.68 (0.82)	-0.14 (+0.03)	nd	Poor

Supplementary table 44. Evidence profile of RCTs examining ACE-I or ARB in biopsy-proven IgA nephropathy

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	0 RCTs	--	--	--	--	--	--	--	Critical
ESRD	1 RCT (High)	109 (55)	Some limitations (-1)	N/A	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Insufficient evidence	Critical
Complete remission	0 RCTs	--	--	--	--	--	--	--	High
Partial remission	0 RCTs	--	--	--	--	--	--	--	High
Relapse	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (categorical)	2 RCTs (High)	104 (52)	No limitations (0)	Important inconsistencies (-1)	Direct (0)	None (0)	Moderate	Benefit for ACE-I or ARB without steroids. No difference with steroids	High
Kidney function (categorical)	3 RCTs (High)	148 (75)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	Benefit for ACE-I or ARB	High
ΔProteinuria (continuous)	4 RCTs (High)	227 (116)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	Benefit for ACE-I or ARB	Moderate
ΔKidney function (continuous)	6 RCTs (High)	424 (213)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	Benefit for ACE-I or ARB	Moderate
Adverse events	2 RCTs	149 (77)						No difference in major adverse event	Moderate

Balance of potential benefits and harm:
Benefit of ACE-I or ARB

Quality of overall evidence:
Moderate

Supplementary table 45. Summary table of RCTs examining ACE-I or ARB in biopsy-proven IgA nephropathy (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
ESRD												
Time to doubling of baseline S_{Cr} or ESRD	Li 2006[50] Hong Kong	2 y (2 y)	Valsartan, 80 mg/d	Placebo	54 (54)	55 (55)	GFR 87 ml/min S_{Cr} 1.11 mg/dl	1.8 g/d	1 (1%) [4 (7%)]	Estimated OR 0.23 (0.03-2.21)	NS (*P* -log-rank test 0.18)	Fair
Proteinuria												
Proteinuria <500 mg/d/1.73 m^2 lasting ≥6 mo (All)	Coppo 2007[17] Europe	38 mo (38 mo)	Benazepril 0.2 mg/kg/d	Placebo	32 (32)	34 (34)	eGFR 116 ml/min/1.73m^2	1.6 g/d	41% [9%]	nd	0.0002	Good
Proteinuria <500 mg/d/1.73 m^2 lasting ≥6 mo (children only)									50% [11%]	nd	nd	
Proteinuria <160 mg/d/1.73 m^2 lasting ≥6 mo (All)									13% [0 (0%)]	--	0.02	
Proteinuria <160 mg/d/1.73 m^2 lasting ≥6 mo (children only)									2 (17%) [0 (0%)]	--	nd	
↓Urine protein ≥50%	Horita 2007[36] Japan	24 mo (24 mo)	Losartan 50 mg/d, prednisone taper	Prednisone taper	20 (20)	18 (18)	GFR 104 ml/min/1.73m^2 S_{Cr} 0.8 mg/dl	1.6 g/d	18 (90%) [15 (83%)]	RR 1.08 (0.84-1.39)[112]	NS (0.551)	Fair
Kidney Function												
↓CrCl 30%	Coppo 2007[17] Europe	38 mo (38 mo)	Benazepril 0.2 mg/kg/d	Placebo	32 (32)	34 (34)	eGFR 116 ml/min/1.73m^2	1.6 g/d	3% [15%]	nd	NS (0.18)	Fair
↓CrCl 30% or ↑proteinuria >3.5 g/d/1.73 m^2									1 (3%) [9 (27%)]	RR 0.12 (0.02-0.88)[113]	NS (0.034)	Good
↑S_{Cr} 50%	Praga	76 mo	ACE-I	No ACE-I	23	21	GFR 102	2 g/d	3 (13%)[114]	RR 0.23	0.010	Good

[112] Calculated by ERT
[113] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
	2003[68] Spain	(76 mo)	5-40 mg/d BP<140/90	BP<140/90	(23)	(21)	ml/min S_{Cr} 1.0 mg/dl	(>3.5 g/d: 11%)	[12 (57%)]	(0.07-0.70)[115]		
		4 y							0 (0%) [~6 (30%)]	--	<0.05	Fair
		7 y							~2 (8%) [~9 (45%)]	RR 0.20 (0.05-0.83)[116]	0.027	Fair
S_{Cr} ≥1.5 mg at last visit		76 mo (76 mo)							3 (13%)[117] [11 (52%)]	RR 0.25 (0.08-0.77)[118]	0.016	Good
↑ S_{Cr} ≥50%	Horita 2007[36] Japan	24 mo (24 mo)	Losartan 50 mg/d, prednisone taper	Prednisone taper	20 (20)	18 (18)	GFR 104 ml/min/1.73m^2 S_{Cr} 0.8 mg/dl	1.6 g/d	nd (0%?) [4 (22%)]	RD -0.22[119]	nd	Poor
Adverse Event												
Major adverse event	Li 2006[50] Hong Kong	2 y (2 y)	Valsartan, 80 mg/d	Placebo	54 (54)	55 (55)	GFR 87 ml/min S_{Cr} 1.11 mg/dl	1.8 g/d	2 (4%) [3 (5%)]	RR 0.68 (0.12-3.91)[120]	NS (0.664)	Good
AE: Postural hypotension	Horita 2007[36] Japan	24 mo (24 mo)	Losartan 50 mg/d, prednisone taper	Prednisone taper	22 (22)	18 (18)	GFR 104 ml/min/1.73m^2 S_{Cr} 0.8 mg/dl	1.6 g/d	2 (9%) [0 (0%)]	RD -0.09[121]	nd	Fair

[114] S_{Cr} at baseline in the three enalapril-treated patients who reached the primary end point were 0.9, 1.4, and 1.4 mg/dl, corresponding to creatinine clearances of 120, 75, and 60 ml/min, respectively.
[115] Calculated by ERT
[116] Calculated by ERT
[117] Same 3 participants as for S_{Cr} 50% increase.
[118] Calculated by ERT
[119] Calculated (P=0.02)
[120] Calculated by ERT
[121] Calculated (NS)

Supplementary table 46. Summary table of RCTs examining ACE-I or ARB in biopsy-proven IgA nephropathy (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
Proteinuria	Li 2006[50] Hong Kong, China	12 wk (2 y)	Valsartan, 80 mg/d	Placebo	54 (54)	55 (55)	GFR 87 ml/min S_{Cr} 1.11 mg/dl	1.8 g/d	g/d	1.80 (2.35)	0.35 (0.19)	0.005	Good
		24 wk (2 y)								1.80 (2.35)	1.0 (0)	<0.001	
		52 wk (2 y)								1.80 (2.35)	0.54 (0.38)	<0.001	
		76 wk (2 y)								1.80 (2.35)	0.46 (0.24)	<0.001	
		104 wk (2 y)								1.80 (2.35)	0.57 (0.38)	<0.001	
Absolute ∆proteinuria		2 y (2 y)								1.80 (2.35)	-0.66 (+0.08)	<0.001	
%∆Proteinuria										1.80 (2.35)	-33.5 (+15.0)	<0.001	
Proteinuria	Praga 2003[68] Spain	76 mo (76 mo)	ACE-I 5-40 mg/d BP<140/90	No ACE-I BP<140/90	23 (23)	21 (21)	GFR 102 ml/min S_{Cr} 1.0 mg/dl	2 g/d (>3.5 g/d: 11%)	g/d	2.0 (1.7)	-1.1 (+0.3)	<0.001	Good
		1 y									-0.8 (-36%) [+0.1 (+23%)]	<0.001	
Proteinuria	Shimizu 2008[73] Japan	6 mo	Losartan	"Antiplatelet agents"	18 (18)	18 (18)	GFR 72 ml/min S_{Cr} 1.0 mg/dl	0.81 g/d	g/d	0.81 (0.73)	-0.36 (-0.10)	NS	Poor
Proteinuria	Horita 2007[36] Japan	24 mo (24 mo)	Losartan 50 mg/d, prednisone taper	Prednisone taper	20 (20)	18 (18)	GFR 104 ml/min/1.73m^2 S_{Cr} 0.8 mg/dl	1.6 g/d	g/24h	1.6 (1.6)	-1.3 (-1.1)	<0.05	Fair
S_{Cr}/GFR/CrCl													
Mean rates of GFR throughout study period	Li 2006[50] Hong Kong, China	2 y (2 y)	Valsartan, 80 mg/d	Placebo	54 (54)	55 (55)	GFR 87 ml/min S_{Cr} 1.11 mg/dl	1.8 g/d	ml/min/y	87 (78)	-5.62 (-6.98)	0.01	Good
Mean rates of GFR 12 to 104 wks										87 (78)	-4.63 (-6.92)	0.019	
CrCl	Praga 2003[68] Spain	76 mo (76 mo)	ACE-I 5-40 mg/d BP<140/90	No ACE-I BP<140/90	23 (23)	21 (21)	GFR 102 ml/min S_{Cr} 1.0 mg/dl	2 g/d (>3.5 g/d: 11%)	ml/min	102 (99)	-7 (-35)	<0.001	Good
S_{Cr}									mg/dl	1.0 (0.9)	+0.2 (+1.0)	<0.001	
∆CrCl	Coppo 2007[17] Europe	38 mo (38 mo)	Benazepril 0.2 mg/kg/d	Placebo	32 (32)	34 (34)	eGFR 116 ml/min/1.73m^2	1.6 g/d/1.73 m^2	ml/min/1.73 m^2	117.2 (118.3)	+8 (-4)	0.03	Good
CrCl	Horita 2007[36]	24 mo (24 mo)	Losartan 50 mg/d,	Prednisone taper	20 (20)	18 (18)	GFR 104 ml/min/1.73m^2	1.6 g/d	ml/min/1.73 m^2	104 (103)	-4 (-19)	NS	Fair

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
S_{Cr}	Japan		prednisone taper				S_{Cr} 0.8 mg/dl		mg/dl	0.8 (0.7)	0 (+0.2)		
CrCl	Shi 2002[72] China	18 mo	ACE-I	Non ACE-I drug	44 (65)	39 (66)	GFR 78 ml/min	1.98 g/d	ml/min	78.55 (78.20)	-9.4 (-7.9)	NS	Poor
S_{Cr}									μmol/L	125.07 (106.55)	Follow-up: -8.01 (+47.85)		
GFR	Shimizu 2008[73] Japan	12 mo (12 mo)	Losartan	"Antiplatelet agents"	18 (18)	18 (18)	GFR 72 ml/min S_{Cr} 1.0 mg/dl	0.81 g/d	ml/min	72.0 (75.4)	-0.2 (+0.7)	NS	Poor
S_{Cr}									mg/dl	1.0 (0.9)	-0.1 (0)	NS	

Supplementary table 47. Evidence profile of RCTs examining steroid regimens in biopsy-proven IgA nephropathy

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability*	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	0 RCTs	--	--	--	--	--	--	--	Critical
ESRD	4 RCTs (High)	336 (164)	Some limitations (-1)	No important inconsistencies (0)	Some uncertainty (-1)	None (0)	Low	Benefit for steroids. No difference between low dose steroid and no steroid in one trial	Critical
Remission	0 RCTs	--	--	--	--	--	--	--	High
Relapse	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (categorical)	3 RCTs (High)	250 (121)	Some limitations (-1)	No important inconsistencies (0)	Some uncertainty (-1)	None (0)	Low	Benefit for steroid[122]	High
Kidney function (categorical)	3 RCTs (High)	179 (90)	Serious limitations (-2)	No important inconsistencies (0)	Some uncertainty (-1)	None (0)	Very low	Benefit for steroids	High
ΔProteinuria (continuous)	6 RCTs (High)	367 (180)	Some limitations (-1)	No important inconsistencies (0)	Some uncertainty (-1)	None (0)	Low	Benefit for steroid[123]	Moderate
∆Kidney function (continuous)	5 RCTs (High)	363 (179)	Some limitations (-1)	No important inconsistencies (0)	Some uncertainty (-1)	None (0)	Low	Benefit of steroids	Moderate
Adverse events	1 RCT	60 (29)						No serious adverse events	Moderate

Balance of potential benefits and harm:
Benefit for steroids

Quality of overall evidence:
Low to Very low

* Generalizability was evaluated with regard to optimized therapy of proteinuria and hypertension with angiotensin converting enzyme (ACE-I) or angiotensin receptor blockage (ARB)

[122] Among patients with a mean proteinuria of 2 g/d.
[123] Among patients with a mean proteinuria of 2 g/d or more.

Supplementary table 48. Meta-analyses and systematic reviews on immunosuppression for IgA nephropathy

Study, Year	Study Eligibility Criteria	Interventions (Studies)	Outcomes	Conclusions	Comments	Yes/No
Samuels 2004[70]	Head-to-head or placebo/no treatment randomized trials evaluating the effects of different immunosuppressive agents with biopsy proven IgA nephropathy. Both Adults and pediatric patients	Efficacy of steroids (7 trials) Efficacy of Immunosuppressive agents + steroids (3 trials) Efficacy of Immunosuppressive agents alone (3 trials)	Risk of ESRD (need for dialysis) Doubling of serum creatinine Glomerular filtration rate (GFR or CrCl) Urinary Protein Excretion (g/24hr)	Use of steroids in IgA nephropathy significantly reduced risk of ESRD, the doubling of serum creatinine, and a significant reduction in urinary protein excretion. Similar efficacy was not noted for kidney function with use of Immunosuppressive agents + steroids or Immunosuppressive agents alone Immunosuppressive agents alone were associated with reduction in urinary protein excretion.	Is Eligibility criteria similar to the guideline	Yes (biopsy proven IgA nephropathy; clinical trials)
Database: Medline, Embase, Cochrane renal registry, ASN conference Proceedings, Experts						
Search Dates: Until 2002					Are there any limitations to systematic review methodology	No
N Studies: 13 trials (16 publications)						
N Subjects: 623					Is limitation to evidence clearly addressed by the authors	Yes
Description of limitations of evidence by authors	Lack of details on adverse events in published studies Significant heterogeneity as a potential source for reduction in urinary protein excretion with Immunosuppressive agents, which had no significant treatment effect on kidney function parameters. Less applicable to early stages of IgA nephropathy Suboptimal quality of trial reporting Insufficient data to explore whether the duration of treatment or disease severity influenced the effect of treatment					

Author, Year, RefID	Intervention	Control	Outcome	Mean follow up	Baseline kidney function/proteinuria	N studies (N intervention group/ total N)	Pooled RR[1](95% CI)	*P*-value	Test for heterogeneity	
									I^2 Statistic	*P*-value
Samuels 2004[70]	Steroid	No treatment/placebo	ESRD	6-130 mo*	**2 studies**: CrCl >25 ml/min/1.73m^2 or >70 ml/min **2 studies**: S_{Cr} >136µmol/L **1 study**: S_{Cr} <132 µmol/L **1 study**: UPE <1.5g/d **1 study**: no data	6 (160/341)	0.44 (0.25, 0.80)	0.007	0%	NS
Study Years : Until 2002	Steroid	No treatment/placebo	Doubling of S_{Cr}			6 (160/341)	0.45 (0.29, 0.69)	0.0003	0%	NS
	Steroid	No treatment/placebo/dipyridamole	GFR			4 (67/138)	WMD 17.87 (4.93, 30.82)	0.007	53.2%	0.09
	Steroid	No treatment/placebo/dipyridamole	Urinary protein excretion (g/24h)			5 (127/263)	WMD −0.49 (−0.72, −0.25)	<0.0001	0%	NS
Comments	The systematic review did not report ACE-I use in the control arm or as co-medications									

* Except for Shoji AJKD 2000, all studies had 6-130 mo follow-up. Shoji 2000 had 3 mo follow-up.
^ Except for Lai BMJ 1987, all studies had 23 mo and 36 mo follow-up. Lai 1987 had 3 mo follow-up.
Errors noted in text (page 179) and figure 6, 7.

Supplementary table 49. Summary table of RCTs examining steroid regimens in biopsy-proven IgA nephropathy (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
ESRD													
Doubling of S_{Cr} or ESRD	Manno 2009[53] Italy	8 y (6 mo)	Prednisone, ramipril Target BP <120–80 mmHg 24-h proteinuria to ≤1.0 g	Ramipril Target BP <120–80 mmHg 24-h proteinuria to ≤1.0 g	48 (48)	49 (49)	GFR 100 ml/min/1.73m^2	1.7 g/d	4 wk wash-out 100%	2 (4%) [13 (27%)]	RR 0.16 (0.04-0.66)[124]	0.011	Good
ESRD										1 (2%) [7 (14%)]	RR 0.15 (0.02-1.14)[125]	NS (0.067)	Good
Kidney survival	Lv 2009[51] China	2 y (nd)	Cilazapril+steroid	Cilazapril	29 (30)	31 (33)	S_{Cr} 1.1 mg/dl GFR 102 ml/min/1.73 m^2	2.0 g/d	4 wk wash-out 100%	28 (97%) [23 (76%)]	RR 1.30 (1.05-1.62)[126]	0.018	Fair
		3 y (nd)								28 (97%) [19 (66%)]	RR 1.58 (1.18-2.10)[127]	0.002	
10-y kidney survival	Pozzi 2004[66] Italy	10 y (6 mo)	Prednisone, anti-HTN, and antiplatelet agents as needed	Anti-HTN, and antiplatelet agents as needed	43 (43)	43 (43)	GFR 93 ml/min S_{Cr} 97·2 µmol/L	2.0 g/d	14%	97% [53%]	RR 0.06 (0.01-0.44)	0.0003	Good
RRT										1 (2%) [5 (12%)]	RR 0.20 (0.02-1.64)[128]	nd	Fair
Kidney survival	Pozzi 1999[65] Italy (Multicenter)	5 y (6 mo)								95% [74%]		0.04	Fair
ESRD	Katafuchi 2003[46] Japan	5 y (2 y)	Low dose steroid, dipyridamole	Dipyridamole	43 (43)	47 (47)	GFR 901 ml/min/1.73 m^2	252 mg/dl	2%	3 (7%) [3 (6%)]	RR 1.09 (0.23-5.13)[129]	NS	Fair
Proteinuria													
↓Proteinuria <1g	Manno 2009[53] Italy	8 y (6 mo)	Prednisone, ramipril Target BP <120–80 mmHg 24-h proteinuria to ≤1.0 g	Ramipril Target BP <120–80 mmHg 24-h proteinuria to ≤1.0 g	48 (48)	49 (49)	GFR 100 ml/min/1.73m^2	1.7 g/24h	4 wk wash-out 100%	36 (75%) [33 (67%)]	RR 1.11 (0.86-1.44)[130]	NS (0.407)	Good

[124] Calculated by ERT
[125] Calculated by ERT
[126] Calculated by ERT
[127] Calculated by ERT
[128] Calculated by ERT
[129] Calculated by ERT
[130] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
↓Proteinuria >50%	Lv 2009[51] China	6 mo (nd)	Cilazapril+steroid	Cilazapril	29 (30)	31 (33)	S_{Cr} 1.1 mg/dl GFR 102 ml/min/1.73 m^2	2.0 g/d	4 wk wash-out 100%	22 (71%) [10 (34%)]	RR 2.35 (1.36-4.08)[131]	nd	Fair
		1 y (nd)								81% (58%)		nd	
Minimal response ↓<1g/d proteinuria	Pozzi 2004[66] Italy	6 mo (6 mo)	Steroids	Supportive therapy	43 (43)	43 (43)	GFR 93 ml/min S_{Cr} 97·2 µmol/L	2.0 g/d	14%	44% [21%]	RR 2.11 (1.08-4.13)	0.037	Good
		1 y (6 mo)								72% [30%]	RR 2.38 (1.46-3.90)	<0.001	
Optimal response ↓<0.5g/d proteinuria		6 mo (6 mo)								19% [5%]	RR 4.00 (0.90-17.76)	NS (0.089)	Good
		1 y (6 mo)								11 (26%) [2 (5%)]	RR 5.50 (1.30-23)	0.014	
Kidney Function													
↓Kidney function, CrCl <60% baseline	Hogg 2006[35] US, Canada	3 y (2 y)	Prednisone taper (80→40 mg every other day	Placebo	30 (30)	29 (29)	GFR 109 ml/min/1.73 m^2	UPCR 2.2	53% [48%]	2 (9.2%[132]) [4 (8.7%)]	HR[133] 0.31 (0.05, 1.8)	NS	Good
Progression of renal disease (↑S_{Cr} 50%)	Pozzi 1999[65] Italy (Multicenter)	5 y (6 mo)	Prednisone, anti-HTN, and antiplatelet agents as needed	Anti-HTN, and antiplatelet agents as needed	43 (43)	43 (43)	GFR 93 ml/min S_{Cr} 97·2 µmol/L	2.0 g/d	14%	9 (21%) [14 (33%)]	RR 0.41 (0.17-0.98)	0.04	Fair
Doubling of S_{Cr} (↑S_{Cr} 100%))	Pozzi 2004[66] Italy	7 y (6 mo)								1 (2%) [13 (30%)]	RR 0.08 (0.01-0.56)[134]	nd	
CKD (↓CrCl>15%)	Lai 1986[48] Hong Kong	3 y (4 mo)	Prednisone	No prednisone	17 (17)	17 (17)	GFR 68 ml/min	6.5 g/d	nd	2 (12%) [3 (18%])	RR 0.67 (0.13-3.50)[135]	nd	Poor
Adverse Events													
Major adverse events	Lv 2009[51] China	7 mo (nd)	Cilazapril+steroid	Cilazapril	29 (30)	31 (33)	S_{Cr} 1.1 mg/dl GFR 102 ml/min/1.73 m^2	2.0 g/d	4 wk wash-out 100%	0 (0%) [0 (0%)]	--	nd	Fair

[131] Calculated by ERT
[132] Estimated cumulative proportion of failures at 3 years
[133] Controlled for baseline UPCR. Both also NS without adjusting for baseline UP/C
[134] Calculated by ERT
[135] Calculated by ERT

Supplementary table 50. Summary table of RCTs examining steroid regimens in biopsy-proven IgA nephropathy (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results			*P* value	Quality
			Intervention	Control	Intervention	Control				Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria														
Time averaged proteinuria	Lv 2009[51] China	1 y (nd)	Cilazapril+steroid	Cilazapril	29 (30)	31 (33)	S_{Cr} 1.1 mg/dl GFR 102 ml/min/1.73 m^2	2.0 g/d	4 wk wash-out 100%	g/d	2.5 (2.0)	-1.5 (-0.4)	0.01	Good
UPCR	Hogg 2006[35] US, Canada	3 y (2 y)	Prednisone taper (80→40 mg every other day	Placebo	30 (30)	29 (29)	GFR 109 ml/min/1.73 m^2	UPCR 2.2	53% [48%]	None	2.2 (1.4)	nd	<0.05	Poor
ΔUrinary protein	Katafuchi 2003[46] Japan	5 y (2 y)	Low dose steroid, dipyridamole	Dipyridamole	43 (43)	47 (47)	GFR 91 ml/min/1.73 m^2	252 mg/dl	2%	mg/dl	252 (143)	-134 (-43)	nd	Fair
↓Proteinuria (median)	Pozzi 1999[65] Italy (Multicenter)	5 y (6 mo)	Prednisone, anti-HTN, and antiplatelet agents as needed	Anti-HTN, and antiplatelet agents as needed	43 (43)	43 (43)	GFR 93 ml/min S_{Cr} 97·2 μmol/l	2.0 g/d	14%	g/d	2.0 (1.8)	-1.2* (-1.0)	<0.05	Fair
ΔProteinuria	Lai 1986[48] Hong Kong	3 y (4 mo)	Prednisone	No prednisone	17 (17)	17 (17)	GFR 68 ml/min	6.5 g/d	nd	g/d	6.5 (4.7)	-3.2 (-1.4)	nd	Poor
ΔProteinuria	Julian, 1993[44] US	1 y (1 y)	Alternate day prednisone	No prednisone	35 (35)		S_{Cr} 135 μmol/l	nd	40%	nd	3.5 (3.2)	-2.2 (-1.4)	nd	Fair
Kidney Function														
Mean rate ↓kidney function	Manno 2009[53] Italy	8 y (6 mo)	Prednisone, ramipril Target BP <120–80 mmHg 24-h proteinuria to ≤1.0 g	Ramipril Target BP <120–80 mmHg 24-h proteinuria to ≤1.0 g	48 (48)	49 (49)	GFR 100 ml/min/1.73m^2	1.7 g/24h	4 wk wash-out 100%	ml/min/ 1.73m^2 /y	100.4 (97.5)	−0.56 (−6.17)	0.013	Good
ΔS_{Cr}	Katafuchi 2003[46] Japan	5 y (2 y)	Low dose steroid, dipyridamole	Dipyridamole	43 (43)	47 (47)	GFR 91 ml/min/1.73 m^2	252 mg/dl	2%	mg/dl	0.95 (0.95)	+0.4 (+0.6)	NS	Fair
S_{Cr}	Hogg 2006[35] US, Canada	3 y (2 y)	Prednisone taper (80→40 mg every other day	Placebo	30 (30)	29 (29)	GFR 109 ml/min/1.73 m^2	UPCR 2.2	53% [48%]	mg/dl	1.0 (0.8)	0 (+0.3)	nd	Poor

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results			*P* value	Quality
			Intervention	Control	Intervention	Control				Units	Baseline Intervention (Control)	Δ Intervention (Control)		
ΔS_{Cr}	Koike 2008[47] Japan	2 y (2 y)	Alternate-day prednisolone 5–10 mg dipyridamole or zilazep 150 or 300 mg/d	Dipyridamole or zilazep 150 or 300 mg/d	24 (24)	24 (24)	S_{Cr} 0.92 mg/dl	0.97 g/d	23%	mg/dl	0.92 (1.15)	0 (+0.03)	NS	Poor
ΔCrCl	Lai 1986[48] Hong Kong	3 y (4 mo)	Prednisone	No prednisone	17 (17)	17 (17)	GFR 68 ml/min	6.5 g/d	nd	ml/min	68.1 (68.2)	+6.0 (-3.6)	nd	Poor
ΔS_{Cr}										µmol/l	115.3 (125.5)	+11.6 (+5.2)		
ΔS_{Cr}	Julian 1993[44] US	1 y (1 y)	Alternate day prednisone	No prednisone	35 (35)		S_{Cr} 135 µmol/l	3.5 g/d	40%	µmol/l	135 (138)	-40 (+19)	NS (0.06)	Fair

* estimated from figure

Supplementary table 51. Meta-analyses and systematic reviews on immunosuppression for IgA nephropathy

Study, Year	Study Eligibility Criteria	Interventions (Studies)	Outcomes	Conclusions	Comments	Yes/No
Samuels 2004[70] Database: Medline, Embase, Cochrane renal registry, ASN conference Proceedings, Experts Search Dates: Until 2002 N Studies: 13 trials (16 publications) N Subjects: 623	Head-to-head or placebo/no treatment randomized trials evaluating the effects of different immunosuppressive agents with biopsy proven IgA nephropathy. Both Adults and pediatric patients	Efficacy of steroids (7 trials) Efficacy of Immunosuppressive agents + steroids (3 trials) Efficacy of Immunosuppressive agents alone (3 trials)	Risk of ESRD (need for dialysis) Doubling of serum creatinine Glomerular filtration rate (GFR or CrCl) Urinary Protein Excretion (g/24hr)	Use of steroids in IgA nephropathy significantly reduced risk of ESRD, the doubling of serum creatinine, and a significant reduction in urinary protein excretion. Similar efficacy was not noted for kidney function with use of Immunosuppressive agents + steroids or Immunosuppressive agents alone Immunosuppressive agents alone were associated with reduction in urinary protein excretion.	Is Eligibility criteria similar to the guideline	Yes (biopsy proven IgA nephropathy; clinical trials)
					Are there any limitations to systematic review methodology	No
					Is limitation to evidence clearly addressed by the authors	Yes
Description of limitations of evidence by authors	Lack of details on adverse events in published studies Significant heterogeneity as a potential source for reduction in urinary protein excretion with Immunosuppressive agents, which had no significant treatment effect on kidney function parameters. Less applicable to early stages of IgA nephropathy Suboptimal quality of trial reporting Insufficient data to explore whether the duration of treatment or disease severity influenced the effect of treatment					

Author, Year, RefID	Intervention	Control	Outcome	Mean follow up	Baseline kidney function/proteinuria	N studies (N intervention group/ total N)	Pooled RR[1](95% CI)	*P*-value	Test for heterogeneity	
									I^2 Statistic	*P*-value
Samuels 2004[70] Study Years: Until 2002	Immunosuppressive agents or cyclosporine alone	No treatment/placebo/dipyridamole	ESRD	24-72 mo	**1 study**: S_{Cr} >130µmol/l **1 study**: well preserved kidney function **1 study**: No clinical inclusion criteria	2 (total 106)	0.35 (0.04, 3.22)	NS	0%	NS
	Immunosuppressive agents or cyclosporine alone	No treatment/placebo/dipyridamole	Urinary protein excretion (g/24hr)			3 (63 / 122)	WMD −0.94 (−1.43, -0.46)	0.0001	48.7%	NS
	Immunosuppressive agents + steroids	No treatment/placebo/dipyridamole	ESRD	23, 36 mo*	**2 studies**: No clinical inclusion criteria **1 study**: Proteinuria >1.5 g/d or CrCl >5 ml/min/1.73m^2	2 (total 152)	0.59 (0.06, 6.03)	NS	nd	nd
	Immunosuppressive agents + steroids	No treatment/placebo/dipyridamole	Urinary protein excretion (g/24hr)			3 (79 / 153)	WMD -1.25 (−2.71, 0.21)	0.09	97.3%	<0.0001
Comments	The systematic review did not report ACE-I use in the control arm or as co-medications									

* Except for Shoji AJKD 2000, all studies had 6-130 mo follow-up. Shoji 2000 had 3 mo follow-up.

^ Except for Lai BMJ 1987, all studies had 23 mo and 36 mo follow-up. Lai 1987 had 3 mo follow-up.

Errors noted in text (page 179) and figure 6, 7.

Supplementary table 52. Summary table of RCTs examining steroid and immunosuppressive regimens in biopsy-proven IgA nephropathy (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR /HR		
ESRD													
Renal survival	Ballardie 2002[6] UK	5 y (2 y)	Prednisolone, cyclophosphamide BP <160/90 mmHg	BP <160/90 mmHg	19 (19)	19 (19)	S_{Cr} >130µmol/l	3.9 g/24h	26%	72% [5%]		0.04	Poor
Proteinuria													
Patients with proteinuria >500 mg/d	Harmankaya 2002[32] Turkey	5 y (4 mo)	Prednisolone, AZA DBP<90 mmHg	DBP<90 mmHg	21 (21)	22 (22)	S_{Cr} 0.8 mg/dl	nd	0%	0 (0%) [3 (14%)]	--	nd	Poor
Adverse events													
AZA and warfarin related AE	Yoshikawa 1999[89] Japan (Multicenter)	2 y (2 y)	Prednisolone, AZA, heparin, warfarin, and dipyridamole	Heparin, warfarin, and dipyridamole	40 (40)	34 (34)	S_{Cr} 0.64 mg/dl	1.35 g/d	0%	Treatment discontinuation due to mild leukopenia or ↑ transaminase n=3 [treatment discontinuation due to bleeding n=2]	--	--	Fair

Supplementary table 53. Summary table of RCTs examining steroid and immunosuppressive regimens in biopsy-proven IgA nephropathy (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results			*P* value	Quality
			Intervention	Control	Intervention	Control				Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria														
↓Proteinuria	Ballardie 2002[6] UK	5 y (2 y)	Prednisolone, cyclophosphamide BP <160/90 mmHg	BP <160/90 mmHg	19 (19)	19 (19)	S_{Cr} >130 µmol/l	3.9 g/24h	26%	g/24h	3.9 (4.6)	-3.6 (-0.63)	nd	Poor
UPE	Yoshikawa 1999[89] Japan (Multicenter)	2 y (2 y)	Prednisolone, AZA, heparin, warfarin, and dipyridamole	Heparin, warfarin, and dipyridamole	40 (40)	34 (34)	S_{Cr} 0.64 mg/dl	1.35 g/d	0%	g/d	1.35 (0.98)	-1.13 (-0.10)	nd	Fair
S_{Cr}/GFR/CrCl														
Rate ↓kidney function	Ballardie 2002[6] UK	5 y (2 y)	Prednisolone, cyclophosphamide BP <160/90 mmHg	BP <160/90 mmHg	19 (19)	19 (19)	S_{Cr} >130 µmol/l	3.9 g/24h	26%	$\mu mol/l^{-1}/d^{-1} \times 10^{-6}$	-5.19 (-4.85)	-1.07 (-5.12)	nd	Poor
ΔS_{Cr}	Harmankaya 2002[32] Turkey	5 y (4 mo)	Prednisolone, AZA DBP<90 mmHg	DBP<90 mmHg	21 (21)	22 (22)	S_{Cr} 0.8 mg/dl	nd	0%	mg/dl	0.8 (0.9)	+0.1 (+0.1)	NS	Poor
CrCl	Yoshikawa 1999[89] Japan (Multicenter)	2 y (2 y)	Prednisolone, AZA, heparin, warfarin, and dipyridamole	Heparin, warfarin, and dipyridamole	40 (40)	34 (34)	S_{Cr} 0.64 mg/dl	1.35 g/d	0%	ml/min per 1.73 m^2	144 (152)	+3 (-7)	NS	Fair

Supplementary table 54. Evidence profile of RCTs examining AZA in combination vs. AZA alone in biopsy-proven IgA nephropathy

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	1 RCT (High)	207 (101)	No limitations (0)	N/A	Direct (0)	Sparse (-1)	Low	No difference	Critical
ESRD	1 RCT (High)	207 (101)	No limitations (0)	N/A	Direct (0)	Sparse (-1)	Low	No difference	Critical
Remission	0 RCTs	--	--	--	--	--	--	--	High
Relapse	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (categorical)	2 RCTs (High)	287 (141)	No limitations (0)	Important inconsistencies (-1)	Direct (0)	None (0)	Moderate	Possible harm	High
Kidney function (categorical)	2 RCTs (High)	287 (141)	No limitations (0)	Important inconsistencies (-1)	Direct (0)	None (0)	Moderate	No difference	High
Proteinuria (continuous)	2 RCTs (High)	287 (141)	No limitations (0)	No inconsistencies (0)	Direct (0)	None (0)	High	No difference	Moderate
ΔKidney function (continuous)	1 RCT (High)	80 (40)	No limitations (0)	N/A	Direct (0)	Sparse (-1)	Moderate	No difference	Moderate
Adverse events	1 RCT	207 (101)						Treatment-related major side effects for AZA	Moderate

Balance of potential benefits and harm:
Possible worsening, more side effects with AZA

Quality of overall evidence:
Low

Supplementary table 55. Summary table of RCTs examining AZA in combination vs. AZA along in biopsy-proven IgA nephropathy (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
Proteinuria													
Proteinuria disappearance (<0.1 g/m^2/d)	Yoshikawa 2006[90] Japan	24 mo (24 mo)	AZA, warfarin, dipyridamole, prednisolone	Prednisolone	39 (40)	39 (40)	GFR 147 ml/min/1.73 m^2 Scr 49 µmol/l	1.30 g/m^2/d	0%	36 (92%) [29 (74%)]	RR 1.24 (1.01-1.52)[136]	0.039	Good
↓Proteinuria >50% from baseline	Pozzi 2010[67] Italy and Switzerland	5 y (6 mo)	AZA, prednisone alternate day	Prednisone alternate day	101 (101)	106 (106)	GFR 66 ml/min/1.73 m^2 Scr 106 µmol/l	2.0 g/d	46%	45 (45%) [53 (50%)]	RR 0.89 (0.67-1.19)[137]	NS	Good
S_{Cr}/GFR/CrCl													
CrCl <60 ml/min/1.73m^2	Yoshikawa 2006[90] Japan	24 mo (24 mo)	AZA, warfarin, dipyridamole, prednisolone	Prednisolone	39 (40)	39 (40)	GFR 147 ml/min/1.73 m^2 Scr 49 µmol/l	1.30 g/m^2/d	0%	0% [0%]	--	NS	Good
↑SCr >50% from baseline	Pozzi 2010[67] Italy and Switzerland	5 y (6 mo)	AZA, prednisone alternate day	Prednisone alternate day	101 (101)	106 (106)	GFR 66 ml/min/1.73 m^2 Scr 106 µmol/l	2.0 g/d	46%	13 (13%) [12 (11%)]	RR 1.14[138] (0.54-2.37)	NS	Good

[136] Calculated by ERT
[137] Calculated by ERT
[138] Calculated by ERT

Supplementary table 56. Summary table of RCTs examining AZA in combination vs. AZA alone in biopsy-proven IgA nephropathy (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results			*P* value	Quality
			Intervention	Control	Intervention	Control				Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria														
UPE	Yoshikawa 2006[90] Japan	2 y (2 y)	AZA, warfarin, dipyridamole, prednisolone	Prednisolone	39 (40)	39 (40)	GFR 147 ml/min/1.73 m^2 Scr 49 µmol/l	1.30 g/m^2/d	0%	g/m^2/d	1.29 (1.16)	-1.19 (-1.04)	NS	Good
UPE	Pozzi 2010[67] Italy and Switzerland	5 y (6 mo)	AZA, prednisone alternate day	Prednisone alternate day	101 (101)	106 (106)	GFR 66 ml/min/1.73 m^2 Scr 106 µmol/l	2.0 g/d	46%	g/d	2.10 (1.95)	-0.94 (-0.97)	NS	Good
S_{Cr}/GFR/CrCl														
CrCl	Yoshikawa 2006[90] Japan	24 mo (24 mo)	AZA, warfarin, dipyridamole, prednisolone	Prednisolone	39 (40)	39 (40)	GFR 147 ml/min/1.73 m^2 Scr 49 µmol/l	1.30 g/m^2/d	0%	ml/min/ 1.73 m^2	148 (156)	+8 (-1)	NS	Good
Biopsy														
Glomeruli showing sclerosis	Yoshikawa 2006[90] Japan	24 mo (24 mo)	AZA, warfarin, dipyridamole, prednisolone	Prednisolone	32 (40)	30 (40)	GFR 147 ml/min/1.73 m^2 Scr 49 µmol/l	1.30 g/m^2/d	0%	%	5.0 (3.1)	-0.4 (+11.5)	nd	Good
Glomeruli showing crescents											17.3 (19.1)	-15.6 (-18.2)	nd	
Glomeruli showing capsular adhesions											5.2 (3.6)	+0.1 (+1.4)	nd	

Supplementary table 57. Evidence profile of RCTs examining MMF in biopsy-proven IgA nephropathy

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	0 RCTs	--	--	--	--	--	--	--	Critical
ESRD	3 RCTs (High)	106 (58)	Some limitations (-1)	Important inconsistencies (-1)	Direct (0)	None (0)	Low	No difference for MMF vs. placebo	Critical
Complete remission	0 RCTs	--	--	--	--	--	--	--	High
Partial remission	0 RCTs	--	--	--	--	--	--	--	High
Relapse	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (categorical)	2 RCTs (High)	72 (37)	Some limitations (-1)	No inconsistencies	Direct (0)	Sparse (-1)	Low	No difference for MMF vs. placebo	High
Kidney function (categorical)	2 RCTs (High)	66 (38)	Some limitations (-1)	Important inconsistencies (-1)	Direct (0)	Sparse (-1)	Very Low	No difference for MMF vs. placebo	High
Proteinuria (continuous)	2 RCTs (High)	74 (41)	Some limitations (-1)	No inconsistencies	Direct (0)	Sparse (-1)	Low	No difference for MMF vs. placebo	Moderate
ΔKidney function (continuous)	2 RCTs (High)	74 (41)	Some limitations (-1)	Important inconsistencies (-1)	Direct (0)	Sparse (-1)	Very Low	No difference for MMF vs. placebo	Moderate
Adverse events	3 RCTs	106 (58)						Dose reduction due to side effects for MMF	Moderate

Balance of potential benefits and harm:
No difference for MMF

Quality of overall evidence:
Low

Supplementary table 58. Meta-analyses and systematic reviews on MMF therapy for IgA nephropathy

Study, Year	Study Eligibility Criteria	Interventions (Studies)	Outcomes	Conclusions	Comments	Yes/No
Xu 2008[86] Database: PubMed, Cochrane (No language restriction) Search Dates: Until April 2008 N Studies: 4 N Subjects: 168	Included: only reports of RCTs that were conducted on adult humans and which used MMF as the intervention. Excluded: Those that did not clearly report the numbers of patients who recovered, deteriorated or had renal-replacement treatment.	MMF 1.5-2.0 g/d (4 studies) Control: steroids (1 study) and placebo (3 studies)	Proteinuria (4 studies) Increase in Serum Creatinine (3 studies) Need for renal replacement (3 studies)	50% Decline Proteinuria: Total events: 61 (MMF), 38 (control) RR 1.37 (0.79, 2.38) 50% Increase in Scr: Total events: 14 (MMF), 10 (control) RR 1.19 (0.62, 2.25) Need for renal replacement therapy: Total events: 10 (MMF), 8 (control) RR: 1.10 (0.46, 2.64) Authors advice against routine use of MMF in IgAN	Is Eligibility criteria similar to the guideline Are there any limitations to systematic review methodology Is limitation to evidence clearly addressed by the authors	Yes No Yes
Description of limitations of evidence by authors	Smaller number of patients Shorter duration of follow-up in a chronic disease condition Both intervention and control groups received ACE-I Studies are need to assess the effects of MMF alone or with ACE-I or ARBs					
Comments	Individual study quality was rated using Jadad criteria of 5 items that ranged from 3-5 No serious side-effects noted from MMF therapy.					

Author, Year	Intervention	Control	Outcome	N studies (N intervention group/ total N)	Treatment duration	Baseline kidney function/Proteinuria	Pooled RR[1](95% CI)	*P*-value	Test for heterogeneity I^2 Statistic	*P*-value
Xu 2008[86]	MMF 1.5-2.0 g/d	Steroids or placebo	50% decline in proteinuria	4 studies (89/168)	18-36 mo	No data available in the systematic review	1.37 (0.79, 2.38)	0.26	75.5%	0.007
			50% Increase in S_{Cr}	3 studies (58/106)			1.19 (0.62, 2.25	0.6	6.8%	0.34
							1.10 (0.46, 2.64)	0.83	0%	0.44
Comments: Both interventions and control groups used ACE-I										

Supplementary table 59. Summary table of RCTs examining MMF in biopsy-proven IgA nephropathy (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
ESRD													
ESRD	Frisch 2005[28] US	2 y (1 y)	MMF 1000 mg 2x/d + ACE-I	Placebo 1000 mg 2x/d + ACE-I	17 (17)	15 (15)	GFR 38 ml/min/1.73m^2	2.7 g/24hr	Total 100%	5 (29%) [2 (13%)]	Adjusted HR 1.74 0.07–42.3	NS	Fair
Cumulative % free of death or ESRD	Maes 2004[52] Belgium	3 y (3 y)	MMF 2 g/d, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	Placebo lactose cap, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	21 (21)	13 (13)	GFR 73 ml/min/1.73 m^2	1.9 g/d	Total 100%[139]	89% [92%]	--	NS	Fair
ESRD	Tang 2005, 2010[79;80] Hong Kong	6 y (6 mo)	MMF 2 g/d ACE-I or ARB for target BP <125/85 mmHg	ACE-I or ARB for target BP <125/85 mmHg	20 (20)	20 (20)	GFR 75 ml/min/1.73 m^2	1.8 g/d	Total 100%	2 (10%) [9 (45%)]	RR 0.22 (0.05- 0.90)[140]	0.015	Fair
Doubling of S_{Cr} or ESRD		18 mo (6 mo)								1 (5%) [3 (15%)]	RR 0.33 (0.04-2.94)	NS (0.323)	Fair
		6 y (6 mo)								3 (15%) [10 (50%)]	RR 0.30 (0.10-0.93)	0.037	Fair
Kidney Function													
↑S_{Cr} 50%	Frisch 2005[28] US	2 y (1 y)	MMF 1000 mg 2x/d + ACE-I	Placebo 1000 mg 2x/d + ACE-I	17 (17)	15 (15)	GFR 38 ml/min/1.73m^2	2.7 g/24hr	Total 100%	5 (29%) [2 (13%)]	Adjusted HR 1.62 (0.07–35.6)	NS	Fair
↑S_{Cr} 0.5 mg/dl										10 (59%) [7 (47%)]	Adjusted HR 2.84 (0.6–14.6)	NS	
↓Inulin clearance ≥ 25%	Maes 2004[52] Belgium	3 y (3 y)	MMF 2 g/d, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	Placebo lactose cap, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	21 (21)	13 (13)	GFR 73 ml/min/1.73 m^2	1.9 g/d	Total 100%[141]	33% [15%]	nd	NS	Fair
↑S_{Cr} ≥ 50%										14% [0 (0%)]	nd	NS	
Proteinuria													

[139] Higher doses of ACE-I in the MMF group
[140] Calculated by ERT
[141] Higher doses of ACE-I in the MMF group

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
↓24 h protein excretion 50%	Frisch 2005[28] US	2 y (1 y)	MMF 1000 mg 2x/d+ ACE-I	Placebo 1000 mg 2x/d + ACE-I	17 (17)	15 (15)	GFR 38 ml/min/1.73m^2	2.7 g/24hr	Total 100%	3 (18%) [2 (13%)]	RR 1.32 (0.25-6.88)[142]	NS (0.739)	Fair
Remission of proteinuria	Tang 2005[79] Hong Kong	18 mo (6 mo)	MMF 2 g/d ACE-I or ARB for target BP <125/85 mmHg	ACE-I or ARB for target BP <125/85 mmHg	20 (20)	20 (20)	GFR 75 ml/min/1.73 m^2	1.8 g/d	Total 100%	16 (80%) [6 (30%)]	RR 2.67 (1.32-5.39)[143]	0.006	Fair
Adverse Event													
Treatment discontinuation	Frisch 2005[28] US	2 y (1 y)	MMF 1000 mg 2x/d+ ACE-I	Placebo 1000 mg 2x/d + ACE-I	17 (17)	15 (15)	GFR 38 ml/min/1.73m^2	2.7 g/24hr	Total 100%	2 (11%) [2 (13%)]	RR 0.88 (0.14-5.52)[144]	NS (0.894)	Fair
MMF dose adjustment due to AE	Tang 2005[79] Hong Kong	18 mo (6 mo)	MMF 2 g/d ACE-I or ARB for target BP <125/85 mmHg	ACE-I or ARB for target BP <125/85 mmHg	20 (20)	20 (20)	GFR 75 ml/min/1.73 m^2	1.8 g/d	Total 100%	Anemia (n=3) Diarrhea (n=1) Infection (n=3)	--	nd	Fair
Adverse event	Maes 2004[52] Belgium	3 y (3 y)	MMF 2 g/d, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	Placebo lactose cap, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	21 (21)	13 (13)	GFR 73 ml/min/1.73 m^2	1.9 g/d	Total 100%[145]	Discontinuation of MMF due to TB (n=1) Dose reduction due to anemia (n=2) Transient leucopenia (n=1) [Placebo pregnancy uneventful n=1 Rectal carcinoma n=1)	--	nd	Fair

[142] Calculated by ERT
[143] Calculated by ERT
[144] Calculated by ERT
[145] Higher doses of ACE-I in the MMF group

Supplementary table 60. Summary table of RCTs examining MMF in biopsy-proven IgA nephropathy (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results			*P* value	Quality
			Intervention	Control	Intervention	Control				Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria														
Mean urine protein loss	Tang 2005 2010[79;80] Hong Kong	18 mo (6 mo)	MMF 2 g/d ACE-I or ARB for target BP <125/85 mmHg	ACE-I or ARB for target BP <125/85 mmHg	20 (20)	20 (20)	GFR 75 ml/min/1.73 m^2	1.8 g/d	Total 100%	g/d	1.8 (1.87)	-0.66 (+0.53)	0.009	Fair
		2y - 6 y (6 mo)									1.8 (1.87)	nd	NS	Poor
ΔProteinuria	Maes 2004[52] Belgium	3 y (3 y)	MMF 2 g/d, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	Placebo lactose cap, (<5 g NaCl/d), ACE-I(aimed BP 125/75 mmHg)	21 (21)	13 (13)	GFR 73 ml/min/1.73 m^2	1.9 g/d	Total 100% [146]	g/d	1.9 1.3	-0.3 (-0.3)	NS	Fair
S_{Cr}/GFR/CrCl														
Annualized median ΔS_{Cr}	Maes 2004[52] Belgium	3 y (3 y)	MMF 2 g/d, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	Placebo lactose cap, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	21 (21)	13 (13)	GFR 73 ml/min/1.73 m^2	1.9 g/d	Total 100% [147]	mg/dl/y	1.46 (1.39)	+0.11 (+0.05)	NS	Fair
ΔInulin clearance										ml/min/1.73 m^2	73 (69)	-13 (-2)	NS	
Annual rates of ΔS_{Cr}	Tang 2005 2009[79;80] Hong Kong	18 mo (6 mo)	MMF 2 g/d ACE-I or ARB for target BP <125/85 mmHg	ACE-I or ARB for target BP <125/85 mmHg	20 (20)	20 (20)	GFR 75 ml/min/1.73 m^2	1.8 g/d	Total 100%	mg/dl/yr	1.53 (1.65)	-0.013 (+0.108)	NS	Good
Annual rates of ΔCrCl		18 mo (6 mo)								ml/min/1.73 m^2	75 (69)	-3.76 (-1.0)	NS	
		6 y (6 mo)										-1.125 (-3.812)	0.021	

[146] Higher doses of ACE-I in the MMF group
[147] Higher doses of ACE-I in the MMF group

Supplementary table 61. Evidence profile of RCTs examining omega-3 fatty acid treatment in IgA nephropathy

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability*	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	0 RCTs	--	--	--	--	--	--	--	Critical
ESRD	2 RCTs (High)	134 (69)	Some limitations (-1)	No important inconsistencies (0)	Some uncertainty (-1)	None (0)	Low	Benefit of purified omega-3 fatty acid	Critical
Remission	0 RCTs	--	--	--	--	--	--	--	High
Relapse	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (categorical)	1 RCT (High)	30 (15)	Some limitations (-1)	N/A	Some uncertainty (-1)	Sparse (-1)	Very low	Benefit of purified omega-3 fatty acid	High
Kidney function (categorical)	3 RCTs (High)	193 (99)	Some limitations (-1)	Important inconsistencies (-1)	Some uncertainty (-1)	None (0)	Very low	Possible benefit of omega-3 fatty acid	High
∆Proteinuria (continuous)	5 RCTs (High)	240 (127)	Some limitations (-1)	No important inconsistencies (0)	Some uncertainty (-1)	None (0)	Low	Possible benefit of omega-3 fatty acid	Moderate
ΔKidney Function (continuous)	6 RCTs (High)	277 (144)	Some limitations (-1)	Important inconsistencies (-1)	Some uncertainty (-1)	None (0)	Very low	Possible benefit of omega-3 fatty acid	Moderate
Adverse events	0 RCTs	--	--	--	--	--	--	--	Moderate

Balance of potential benefits and harm:
Benefit of omega-3 fatty acid

Quality of overall evidence:
Low to very low

* Generalizability was evaluated with regard to optimized therapy of proteinuria and hypertension with angiotensin converting enzyme (ACE-I) or angiotensin receptor blockage (ARB)

Supplementary table 62. Meta-analyses and systematic reviews on fish oil treatment in IgA nephropathy

Study, Year, RefID	Study Eligibility Criteria	Interventions (Studies)	Outcomes	Conclusions	Comments	Yes/No
Strippoli 2003[76] Database: Medline, EMBASE, Cochrane Renal Registry Search Dates: Until 2002 N Studies: Total 10 Fish oil 3 N Subjects: Fish oil 87	RCTs and quasi RCTs evaluating the effects of different treatment regimens for IgA nephropathy on kidney function and proteinuria	Fish oil (3 studies)	Deterioration in kidney function: 50% increase in serum creatinine level from baseline value or serum creatinine level >1.5 mg/dl [132.6 µmol/l] at end of treatment or reaching ESRD requiring dialysis therapy or transplantation at any time during treatment Daily proteinuria: grams of protein per 24 hours	Fish oils are not beneficial in IgA nephropathy.	Is Eligibility criteria similar to the guideline Are there any limitations to systematic review methodology Is limitation to evidence clearly addressed by the authors	yes no yes
Description of limitations of evidence by authors	Suboptimal reporting of quality of individual trials Language restrictions may have limited the results Inclusion of RCTs and peer reviewed publication may have led to conclusions contrary to the evidence based recommendations published in 1997, and 1999.					

¥ Only data for the fish oil intervention is extracted. For steroids and Immunosuppressive agents, more recent/comprehensive review by Samuels 2004 is selected.

Author, Year, RefID	Intervention	Control	Outcome	N studies (N intervention group/ total N)	Weighted mean Follow-up	Baseline kidney function/Proteinuria	Pooled RR[1](95% CI)	*P*-value	Test for heterogeneity I^2 Statistic	*P*-value
Strippoli 2003[76]¥ Study Years : until 2002	Fish oil	None/ corn oil/olive oil	Kidney function	2 (60/120)	20.7 mo	**1 study**: normal or impaired S_{Cr} (but <4.0 mg/dl) or absence and presence of proteinuria **1 study**: S_{Cr} <3.0 mg/dl or daily proteinuria >1 g **1 study**: Daily proteinuria >0.5 g	0.63 (0.30, 1.31)	NS	nd	0.09
	Fish oil	None/ corn oil/olive oil	S_{Cr}	3 (47/92)			WMD −0.12 (−0.50, 0.25)	NS	nd	0.01
	Fish oil	None/ corn oil/ olive oil	Proteinuria	2 (Total 137)			WMD −0.57 (−1.59, 1.45)	NS	nd	0.09

¥ Only data for the fish oil intervention is extracted. For steroids and Immunosuppressive agents, more recent/comprehensive review by Samuels 2004 is selected.

Supplementary table 63. Summary table of RCTs examining omega-3 fatty acids in biopsy-proven IgA nephropathy (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
ESRD													
ESRD	Alexopoulos 2004[2] Greece	4 y (4 y)	Purified omega-3 fatty acids 3g/d	Supportive therapy (not described)	14 (18)	14 (16)	S_{Cr} 2.2 mg/dl GFR 48 ml/min	2.0 g/d	61% [31%]	1 (7%) [6 (43%)]	RR 0.15 (0.02-1.10)[148]	NS (0.062)	Fair
Cumulative % of death or ESRD	Donadio 1994[20] Multicenter	2 y (2 y)	Fish oil 12 g, ACE-I for target BP 140/85 mmHg	Olive oil ACE-I for target BP 140/85 mmHg	55 (55)	51 (51)	GFR 82 ml/min/1.73m^2 S_{Cr} 1.4 mg/dl	2.5 g/d	Total 61%	5 (10%) [14 (40%)]	RR 0.33 (0.13-0.85)[149]	0.022	Fair
Proteinuria													
%↓Proteinuria	Ferraro 2009[25] Italy	6 mo (6 mo)	Purified omega-3 fatty acids 3 g/d, ramipril 10 mg/d, irbesartan 300 mg/d	Ramipril 10 mg/d, irbesartan 300 mg/d	15 (15)	15 (15)	GFR 91 ml/min	1.3 g/d	Total 100%	11 (73%) [2 (11%)]	RR 0.92 (0.62-1.36)[150]	NS (0.667)	Fair
↓Proteinuria ≥50%										12 (80%) [3 (20%)]	RR 4.0 (1.4-11.3)	0.002	Fair
Kidney Function													
↑S_{Cr} >50%	Alexopoulos 2004[2] Greece	4 y (4 y)	Purified omega-3 fatty acids 3 g/d	Supportive therapy (not described)	14 (18)	14 (16)	S_{Cr} 2.2 mg/dl GFR 48 ml/min	2.0 g/d	61% [31%]	1 (7%) [6[43%]]	RR 0.15 (0.02-1.10)[151]	NS (0.077)	Fair
↓GFR <50%										1 (7%) [7 (50%)]	RR 0.13 (0.02-0.92)[152]	0.041	Fair
↓CrCl <60%	Hogg 2006[35] US, Canada	3 y (2 y)	Fish oil 4 g/d	Placebo	30 (30)	29 (29)	GFR 109 ml/min/1.73 m^2	2.1 g/d	53% [48%]	8 (19%) [4 (9%)]	HR 1.3 (0.4, 4.5)	NS	Good
↓CrCl <60% SUBGROUP					23 (23)	13 (13)	nd	UP/C 1-3		6 (24%) [2 (16%)]	RR 1.70 (0.40-7.22)[153]	NS (0.438)	Fair
↑Scr ≥50%	Donadio 1994[20] Multicenter	2 y (2 y)	Fish oil 12 g, ACE-I for target BP 140/85 mmHg	Olive oil ACE-I for target BP 140/85 mmHg	55 (55)	51 (51)	GFR 82 ml/min/1.73m^2 S_{Cr} 1.4 mg/dl	2.5 g/d	Total 61%	3 (6%) [14 (33%)]	RR 0.20 (0.06-0.65)[154]	0.008	Fair

[148] Calculated by ERT
[149] Calculated by ERT
[150] Calculated by ERT
[151] Calculated by ERT
[152] Calculated by ERT
[153] Calculated by ERT
[154] Calculated by ERT

Supplementary table 64. Summary table of RCTs examining omega-3 fatty acids in biopsy-proven IgA nephropathy (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results			*P* value	Quality
			Intervention	Control	Intervention	Control				Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria														
Proteinuria	Alexopoulos 2004[2] Greece	4 y (4 y)	Purified omega-3 fatty acids 3 g/d	Supportive therapy (not described)	14 (18)	14 (16)	S_{Cr} 2.2 mg/dl GFR 48 ml/min	2.0 g/d	61% [31%]	g/d	2.0 (1.6)	-1.2 (-0.7)	nd	Fair
Annual Δproteinuira											2.0 (1.6)	-0.70 [-0.19]	<0.04	Fair
UPE	Ferraro 2009[25] Italy	6 mo (6 mo)	Purified omega-3 fatty acids 3 g/d, ramipril 10 mg/d, irbesartan 300 mg/d	Ramipril 10 mg/d, irbesartan 300 mg/d	15 (15)	15 (15)	GFR 91 ml/min	1.3 g/d	Total 100%	g/d	1.3 (1.5)	-9.4 (-0.9)	<.001	Fair
UPCR	Hogg 2006[35] US, Canada	2 y (2 y)	Fish oil 4 g/d	Placebo	30 (30)	29 (29)	GFR 109 ml/min/1.73 m^2	2.1 g/d	53% [48%]	--	2.1 (1.4)	nd	NS (0.10)	Poor
Median annual ΔUPE	Donadio 1994[20] Multicenter	2 y (2 y)	Fish oil 12 g, ACE-I for target BP 140/85 mmHg	Olive oil ACE-I for target BP 140/85 mmHg	55 (55)	51 (51)	GFR 82 ml/min/1.73m^2 S_{Cr} 1.4 mg/dl	2.5 g/d	Total 61%	g/d	2.5 3.2	-0.23 (-15%) (-0.10 (-7%)	NS	Fair
ΔProteinuria	Pettersson, 1994[61] Sweden	6 mo (6 mo)	Fish oil 6 g	Corn oil 6 g	15 (15)	17 (17)	Cr-EDTA 63 ml/min/1.73m^2	1.8 g/d	40% [59%]	g/d	1.8 (2.0)	-0.1 (-0.2)	NS	Fair
Kidney Function														
S_{Cr}	Alexopoulos 2004[2] Greece	4 y (4 y)	Purified omega-3 fatty acids 3 g/d	Supportive therapy (not described)	14 (18)	14 (16)	S_{Cr} 2.2 mg/dl GFR 48 ml/min	2.0 g/d	61% [31%]	mg/dl	2.2 (2.8)	+0.1 (+3.1)	nd	Fair
Annual ΔS_{Cr}											2.2 (2.8)	0.2 [0.1]	<0.01	Fair
GFR										ml/min	46 (45)	-5 (-11)	nd	Fair
Annual ΔGFR											46 (45)	-1.4 [-3.0]	<0.001	Fair
eGFR	Ferraro 2009[25] Italy	6 mo (6 mo)	Purified omega-3 fatty acids 3 g/d, ramipril 10 mg/d, irbesartan 300 mg/d	Ramipril 10 mg/d, irbesartan 300 mg/d	15 (15)	15 (15)	GFR 91 ml/min	1.3 g/d	Total 100%	ml/min	91 (73)	+3.3 (-5.1)	NS (0.1)	Fair
S_{Cr}	Hogg 2006[35] US, Canada	2 y (2 y)	Fish oil 4 g/d	Placebo	30 (30)	29 (29)	GFR 109 ml/min/1.73 m^2	2.1 g/d	53% [48%]	mg/dl	0.9 (0.8)	0 +0.2 +0.3	nd	Poor

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results			*P* value	Quality
			Intervention	Control	Intervention	Control				Units	Baseline Intervention (Control)	Δ Intervention (Control)		
CrCl	Bennett 1989[7] Australia	2 y (2 y)	Fish oil 10g/d	No fish oil	17 (17)	20 (20)	S_{Cr} 0.09 – 0.2 mmol/l	1.3 – 2.5 g/d	nd	ml/min	80 76	-23 (-21)	nd	Poor
Annual median ΔS_{Cr}	Donadio 1994[20] Multicenter	2 y (2 y)	Fish oil 12 g, ACE-I for target BP 140/85 mmHg	Olive oil ACE-I for target BP 140/85 mmHg	55 (55)	51 (51)	GFR 82 ml/min/1.73m² S_{Cr} 1.4 mg/dl	2.5 g/d	Total 61%	mg/dl	1.4 (1.5)	+0.03 (+0.14)	0.001	Fair
Annual median ΔCrCl										ml/min/ 1.73m²	82 (81)	-0.3 (-7.1)	0.009	
ΔS_{Cr}	Pettersson 1994[61] Sweden	6 mo (6 mo)	Fish oil 6 g	Corn oil 6 g	15 (15)	17 (17)	Cr-EDTA 63 ml/min/1.73m²	1.8g/d	40% [59%]	µmol/l	131 (120)	+8 (+1)	nd	Fair
ΔCrCl										ml/min	91 (99)	-12 (0)	<0.01	
Annual rate ↓GFR										ml/min/ 1.73m²	63 (59)	-4 (-1)	<0.05	

Supplementary table 65. Meta-analyses and systematic reviews on antiplatelet therapy for IgA nephropathy

Study, Year	Study Eligibility Criteria	Interventions (Studies)	Outcomes	Conclusions	Comments	Yes/No
Taji 2006[78] Database: Medline, Cochrane, EMBASE, Ityu-shi (Japanese medical database) Search Dates: 1970-2005 N Studies: 7 N Subjects: 458	Included: Studies of antiplatelet intervention with a concurrent control group, Human adults, prospective studies. Studies that used cytotoxic agents or steroids in both arms were included. Excluded: Studies that did not clearly report data on the number of patients, dialysis population, and those with cytotoxic agents or steroids in only one arm.	Dipyridamole (5) Dilazep (1) Aspirin (1 study included both dipyridamole and aspirin) Trimetazidine dihydrochloride (1)	Level of proteinuria Renal function (introduction of RRT, creatinine clearance, serum creatinine) Side effects	Antiplatelet agents resulted in reduced proteinuria and protected renal function in patients with IgA nephropathy. Headache was reported in the dipyridamole group in one study.	Is eligibility criteria similar to the guideline Are there any limitations to systematic review methodology Is limitation to evidence clearly addressed by the authors	No (we only include only RCTs for this topic) Yes Yes
Description of limitations of evidence by authors	Suboptimal quality of individual controlled trials Most studies did not assess true outcome of renal death Long-term follow-up studies may yield different set of results The effect of antiplatelet agents alone could not be discerned because patients received other concomitant therapies.					

Author, Year, RefID	Intervention	Control	Outcome	N studies (N intervention group/ total N)	Mean Follow-up	Baseline Kidney function/Proteinuria	Pooled RR[1](95% CI)	*P*-value	Test for heterogeneity I² Statistic	Test for heterogeneity *P*-value
Taji 2006 [78] Study Years : 1970-2005	Any antiplatelet therapy	Placebo/no treatment/carbazochrome	Proteinuria	5 (218/399)	6-60 mo*	**2 studies**: Moderate to severe stage (lab or biopsy diagnosis) **5 studies**: Either UPE in the range of 1.1-2.0 g/d Or CCr 51-88 ml/min	0.61 (0.39, 0.94)	0.03	nd	0.007
	Any antiplatelet therapy	Placebo/no treatment/carbazochrome	Renal function	6 (161/261)			0.74 (0.63, 0.87)	0.0	nd	NS
	Any antiplatelet therapy	Placebo/no treatment/carbazochrome	Proteinuria	5 (218/399)			ARR 0.26 NNT 3.9			
	Any antiplatelet therapy	Placebo/no treatment/carbazochrome	Renal function	6 (161/261)			ARR 0.18 NNT 5.4			
	Dipyridamole	Placebo/no treatment/carbazochrome	Proteinuria	3 (92/182)			0.50 (0.36, 0.69)	0.0	nd	NS
	Dipyridamole	Placebo/no treatment/carbazochrome	Renal function	4 (75/155)			0.69 (0.52, 0.92)	0.01	nd	0.1

* Except for Yagami 1986 Tokai J Exp Clin Med, studies had a range 6-60 mo follow-up. Yagami 1986 had 3.4 mo follow-up

Supplementary table 66. Summary table of RCT examining immunosuppression and anti-platelets in biopsy-proven IgA nephropathy (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
ESRD												
ESRD	Walker 1990[83] Australia	5 y (2 y)	Cyclophosphamide 1-2 mg/kg/d, dipyridamole 400 mg/d, warfarin	No treatment	25 (25)	27 (27)	S_{Cr} 0.10 mmol/l	1.67 g/d	1 (4%) [2 (7%)]	RR 0.54 (0.05-5.59)[155]	NS (0.605)	Fair
Adverse events												
In treatment group	Walker 1990[83] Australia	5 y (2 y)	Cyclophosphamide 1-2 mg/kg/d, dipyridamole 400 mg/d, warfarin	No treatment	25 (25)	27 (27)	S_{Cr} 0.10 mmol/l	1.67 g/d	Amenorrhea (n=1) Oligospermia (n=1) Hematuria (n=1) Hemiplegic migrainous episode (n=1)	--	nd	Fair

[155] Calculated by ERT

Supplementary table 67. Summary table of RCT examining immunosuppression and anti-platelets in biopsy-proven IgA nephropathy (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
ΔUPE	Walker 1990[83] Australia	5 y (2 y)	Cyclophosphamide 1-2 mg/kg/d, dipyridamole 400 mg/d, warfarin	No treatment	25 (25)	27 (27)	S_{Cr} 0.10 mmol/l	1.67 g/d	g/d	1.67 (1.76)	-0.53 (+0.13)	nd	Fair
S_{Cr}/GFR/CrCl													
ΔS_{Cr}	Walker 1990[83] Australia	5 y (2 y)	Cyclophosphamide 1-2 mg/kg/d, dipyridamole 400 mg/d, warfarin	No treatment	25 (25)	27 (27)	S_{Cr} 0.10 mmol/l	1.67 g/d	mmol/l	0.10 (0.12)	+.02 (+.01)	nd	Fair

Supplementary table 68. Summary table of RCT examining antiplatelet treatments in biopsy-proven IgA nephropathy (continuous outcomes)*

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
S_{Cr}/GFR/CrCl													
Slope 1/cr v time plots	Chan 1987[9] Hong Kong	~3 y (nd)	Slow release aspirin 650 mg/d, dipyridamole 25-75 mg 3x/d	Vitamin B complex	19 (19)	19 (19)	S_{Cr} 77 ml/min	1.57 g	none	-0.088 (0.001)	-0.008 (+0.0007)	NS	Fair
S_{Cr}									mmol/l	0.125 (0.13)	+0.073 (+0.069)	NS	
CrCl									ml/min	77 (73)	+1 (-1)	NS	

* Based on discussions with WGM, the only Medline indexed study was data extracted.

Supplementary table 69. Summary table of RCTs examining miscellaneous treatments in biopsy-proven IgA nephropathy (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
Partial remission												
Patients showing normal urine	Yoshikawa 1997[91] Japan	2 y (2 y)	Sairei-to	Control	46 (50)	48 (51)	GFR 130 ml/min/1.73m^2 S_{Cr} 0.59 mg/dl	0.39 g/d	21 (46%) [5 (10%)]	RR 4.38 (1.80-10.65)[156]	<0.001	Fair
Proteinuria												
↓Urine protein ≥50%	Chen 2004[13] China	1 y (1 y)	Urokinase 100,000 IU i.v. 10 d/mo, benazepril 10 mg/d	Benazepril 10 mg/d	35 (35)	36 (36)	S_{Cr} 107 µmol/l	1.82 g/d	25 (71%) [16 (44%)]	RR1.6 (1.05-2.45)[157]	0.027	Fair
Kidney function												
↑S_{Cr} ≥50%	Chen 2004[13] China	1 y (1 y)	Urokinase 100,000 IU i.v. 10 d/mob benazepril 10 mg/d	Benazepril 10 mg/d	35 (35)	36 (36)	S_{Cr} 107 µmol/l	1.82 g/d	0 (0%) [3 (8%)]	--	nd	Fair

[156] Calculated by ERT
[157] Calculated by ERT

Supplementary table 70. Summary table of RCTs examining miscellaneous treatments in biopsy-proven IgA nephropathy (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
Urine protein	Chen 2004[13] China	1 y (1 y)	Urokinase 100,000 IU i.v. 10 d/mo, benazepril 10 mg/d	Benazepril 10 mg/d	35 (35)	36 (36)	S_{Cr} 107 μmol/l	1.82 g/d	g/24h	1.82 (1.79)	-1.20 (-0.50)	<0.05	Fair
Urinary protein	Kano 2003[45] Japan	1 y (1 y)	Fluvastatin 20 mg, dipyridamole 5 mg/kg	Dipyridamole 5 mg/kg	15 (15)	15 (15)	GFR 108 ml/min/1.73 m^2 S_{Cr} 47 μmol/l	1.3 g/24 h/1.73 m^2	g/24 h/1.73 m^2	1.3 (1.2)	-0.2 (+0.1)	NS	Fair
UPE	Frasca 1997[27] Italy	2 y (2 y)	Defibrotide 10mg/kg/d, prednisolone 0.5 mg/kg/alternate day	Prednisolone 0.5 mg/kg/alternate day	10 (10)	10 (10)	GFR 56 ml/min S_{Cr} 1.84 mg/dl	1.0 g/d	g/d	1.0 (0.7)	-0.6 (+0.2)	0.02	Poor
S_{Cr}/GFR/CrCl													
CrCl	Chen 2004[13] China	1 y (1 y)	Urokinase 100,000 IU i.v. 10 d/mo, benazepril 10 mg/d	Benazepril 10 mg/d	35 (35)	36 (36)	S_{Cr} 107 μmol/l	1.82 g/d	ml/min	78.9 (81.6)	+2.9 (-10.0)	<0.05	Fair
S_{Cr}									μmol/l	107 (112)	-1.0 (+33.3)	NS	
CrCl	Kano 2003[45] Japan	1 y (1 y)	Fluvastatin 20 mg, dipyridamole 5 mg/kg	Dipyridamole 5 mg/kg	15 (15)	15 (15)	GFR 108 ml/min/1.73 m^2 S_{Cr} 47 μmol/l	1.3 g/24 h/1.73 m^2	ml/min/1.73 m^2	107.9 (113.2)	+25.2 (-2.7)	0.001	Fair
S_{Cr}									μmol/l	46.9 (45.1)	-5.4 (+3.5)	NS	
%ΔGFR	Frasca 1997[27] Italy	2 y (2 y)	Defibrotide 10mg/kg/d, prednisolone 0.5 mg/kg/alternate day	Prednisolone 0.5 mg/kg/alternate day	10 (10)	10 (10)	GFR 56 ml/min S_{Cr} 1.84 mg/dl	1.0 g/d	ml/min/1.73m^2	56 (64)	+14% (-12%)	0.003	Poor
%ΔS_{Cr}									mg/dl	1.8 (1.7)	-14% (+9%)	0.007	

Supplementary table 71. Evidence profile of RCTs of MMF vs. Cyc for induction therapy in lupus nephritis

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	5 RCTs (High)	618 (307)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	No difference	Critical
ESRD	2 RCTs (High)	184 (90)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Low	No difference	Critical
Remission	6 RCTs (High)	683 (340)	Some limitations (-1)	Important inconsistencies (-1)	Direct (0)	None (0)	Low	Possible benefit for MMF[158]	High
Relapse	1 RCT (High)	140 (71)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	No difference	High
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Kidney function (categorical)	0 RCTs	--	--	--	--	--	--	--	High
ΔProteinuria (continuous)	4 RCTs (High)	152 (123)	Some limitations (-1)	No important inconsistencies/ (0)	Direct (0)	None (0)	Moderate	No difference	Moderate
ΔKidney function (continuous)	4 RCTs (High)	152 (123)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	No difference	Moderate
Adverse events	6 RCTs (High)	683 (340)						More alopecia and infections with cyclophosphamide.	Moderate
		Balance of potential benefits and harm: No difference						**Quality of overall evidence:** Low	

[158] Four of the 6 trials showed no benefit with MMF for complete remission when used for induction therapy. Two trials show increased probability of complete remission with MMF. Three of the 4 trials did not show a benefit with MMF for partial remission when used for induction therapy. One trial showed MMF is more likely to induce partial remission.

Supplementary table 72. Summary table of RCTs examining MMF vs. i.v. Cyc for induction therapy in patients with lupus nephritis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
Mortality													
Death	Appel 2009[3] Multicenter	6 mo (6 mo)	MMF	i.v. Cyc	184 (185)	180 (185)	S_{Cr} 1.1 mg/dl	4.1 g/d	White 40% Asian 33% Other 27%	9 (5%) [5 (3%)]	RR 1.76 (0.60-5.15)[159]	NS (0.29)	Good
Death	Wang 2007[85] China	6 mo (6 mo)	MMF	i.v. Cyc	9 (9)	11 (11)	S_{Cr} 1.65 mg/dl	4.7 g/24h	nd	0 (0%) [0 (0%)]	--	NS	Poor
Death	Ginzler 2005[29] US	6 mo (6 mo)	MMF	i.v. Cyc	71 (71)	69 (69)	S_{Cr} 1.06 mg/dl	4.1 g/d	Black 61% White 17% Hispanic 14% Asian 8%	4 (6%) [8 (3%)]	RR 0.49 (0.15-1.54)[160]	nd	Good
		36 mo (6 mo)								4 (6%) [8 (11%)]	RR 0.48 (0.15-1.60)	nd	Good
Death	Ong 2005[60] Malaysia	6 mo (6 mo)	MMF	i.v. Cyc	19 (26)	25 (28)	S_{Cr} 96.5 µmol/l GFR 97 ml/min	1.8 g/d	Malaysian 42% Chinese 53% Indian 5%	0 (0%) [0 (0%)]	--	NS	Fair
		36 mo (6 mo)								1 (6%) [1 (6%)]	RR 1.32 (0.09-19.71)[161]	NS (0.88)	Fair
Death	El-Shafey 2010[24] Egypt	6 mo (6 mo)	MMF	i.v. Cyc	24 (24)	23 (23)	S_{Cr} 132 µmol/l GFR 73.8 ml/min	1.98.g/d	Egyptian 100%	0 (0%) [1 (4%)]	--	nd	Good
RRT													
Renal failure	Ginzler 2005[29] US	36 mo (6 mo)	MMF	i.v. Cyc	71 (71)	69 (69)	S_{Cr} 1.06 mg/dl	4.1 g/24h	Black 61% White 17% Hispanic 14% Asian 8%	4 (6%) [7 (10%)]	RR 0.53 (0.15-1.81)	nd	Fair
ESRD	Ong 2005[60] Malaysia	6 mo (6 mo)	MMF	i.v. Cyc	19 (26)	25 (28)	S_{Cr} 96.5 µmol/l GFR 97 ml/min	1.8 g/d	Malaysian 42% Chinese 53% Indian 5%	1 (4%) [0 (0%)]	--	nd	Fair
Remission													
Complete remission	Appel 2009[3] Multicenter	6 mo (6 mo)	MMF	i.v. Cyc	185 (185)	185 (185)	S_{Cr} 1.1 mg/dl	4.1 g/d	White 40% Asian 33% Other 27%	16 (9%) [15 (8%)]	RR 1.07 (0.54-2.09)[162]	nd	Good
Complete remission	Wang 2007[85] China	6 mo (6 mo)	MMF	i.v. Cyc	9 (9)	11 (11)	S_{Cr} 1.65 mg/dl	4.70 g/24h	nd	4 (44%) [0 (0%)]	--	0.026	Poor
Partial remission		3 mo (6 mo)								4 (44%) [0 (0%)]	--	0.026	Poor
Partial remission		6 mo (6 mo)								2 (22%) [3 (27%)]	RR 0.81 (0.19-3.87)[163]	nd	Poor

[159] Calculated by ERT
[160] Calculated by ERT
[161] Calculated by ERT
[162] Calculated by ERT
[163] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
Complete remission	Chan 2005[12] China	6 mo (6 mo)	MMF	Cyc	32 (33)	30 (31)	S_{Cr} 1.28 mg/dl GFR 72 ml/min	5.32 g/24h	nd	24 (73%) [23 (74%)]	RR 0.98 (0.74-1.30) [164]	NS	Fair
Partial remission										24% [23%]	--	NS	Fair
Complete remission	Ong 2005[60] Malaysia	6 mo (6 mo)	MMF	i.v. Cyc	19 (26)	25 (28)	S_{Cr} 96.5 µmol/l GFR 97 ml/min	1.8 g/d	Malaysian 42% Chinese 53% Indian 5%	5 (26%) [3 (12%)]	RR 2.19 (0.60-8.06) [165]	NS (0.22)	Fair
Complete remission	Ginzler 2005[29] US	6 mo (6 mo)	MMF	i.v. Cyc	71 (71)	69 (69)	S_{Cr} 1.06 mg/dl	4.1g/d	Black 61% White 17% Hispanic 14% Asian 8%	16 (23%) [4 (6%)]	RR 3.89 (1.37-11.05) [166]	nd	Good
Partial remission										21 (30%) [17 (25%)]	RR 1.20 (0.69-2.07) [167]	nd	Good
Complete remission	El-Shafey 2010[24] Egypt	6 mo (6 mo)	MMF	i.v. Cyc	24 (24)	23 (23)	S_{Cr} 132 µmol/l GFR 73.8 ml/min	1.98.g/d	Egyptian 100%	6 (25%) [5 (23%)]	RR 1.15 (0.41-3.25) [168]	NS (0.53)	Good
Partial remission										8 (33%) (7 (30%)]	RR 1.10 (0.47-2.35) [169]	NS (0.54)	Good
Relapse													
First renal flare after induction therapy	Ginzler 2005[29] US	36 mo (6 mo)	MMF	i.v. Cyc	71 (71)	69 (69)	S_{Cr} 1.06 mg/dl	4.1 g/24h	Black 61% White 17% Hispanic 14% Asian 8%	8 (11%) [8 (11%)]	RR 0.98 (0.37-2.61)	nd	Fair
Adverse Events													
Infections	Appel 2009[3] Multicenter	6 mo (6 mo)	MMF	i.v. Cyc	185 (185)	185 (185)	S_{Cr} 1.1 mg/dl	4.1 g/d	White 40% Asian 33% Other 27%	126 (69%) [111 (62%)]	--	NS (0.17)	Good
GI disorders										61% [67%]	--	nd	Good
Alopecia										20 (11%) [64 (40%)]	RR 0.31 (0.20-0.49) [170]	nd	Good
Severe infections	Ginzler 2005[29] US	6 mo (6 mo)	MMF	i.v. Cyc	71 (71)	69 (69)	Scr 1.06 mg/dl	4.1 g/d	Black 61% White 17% Hispanic 14%	1 (1%) [6 (9%)]	RR 0.16 (0.02-1.31) [171]	nd	Good

[164] Calculated by ERT
[165] Calculated by ERT
[166] Calculated by ERT
[167] Calculated by ERT
[168] Calculated by ERT
[169] Calculated by ERT
[170] Calculated by ERT
[171] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
Pyogenic infections									Asian 8%	nd	RR 0.36	0.03	Good
Amenorrhea										0 (0%) [2 (3%)]	--	nd	Good
Alopecia										0 (0%) [8 (11%)]	--	nd	Good
Lymphopenia										18 (22%) [28 (37%)]	RR 0.62 (0.38-1.02) [172]	nd	Good
Leukopenia	Ong 2005[60] Malaysia	6 mo (6 mo)	MMF	i.v. Cyc	19 (26)	25 (28)	S_{Cr} 96.5 µmol/l GFR 97 ml/min	1.8 g/d	Malaysian 42% Chinese 53% Indian 5%	37% [52%]	--	NS (0.32)	Fair
Oligo-menorrhea										0 (0%) [1 (4%)]	--	nd	Fair
Pneumonia/ septicemia										3 (16%) [3 (12%)]	--	NS	Fair
GI AE, episodes/pt. mo										0.08 [0.07]	--	NS (0.68)	Fair
Herpes zoster	Wang 2007[85] China	6 mo (6 mo)	MMF	i.v. Cyc	9 (9)	11 (11)	S_{Cr} 1.65 mg/dl	4.70 g/24h	nd	1 (11%) [7 (64%)]	RR 0.17 (0.03-1.17)[173]	0.025	Poor
Leukopenia										0 (0%) [2 (18%)]	--	nd	Poor
GI symptoms										0 (0%) [3 (27%)]	--	nd	Poor
Elevated LFTs										0 (0%) [1 (9%)]	--	nd	Poor
GI symptoms	Hu 2002[40] China	6 mo (6 mo)	MMF	Cyc	23 (23)	23 (23)	S_{Cr} 178.9 µmol/l	3.88 g/d	nd	6 (26%) [10 (44%)]	RR 0.60 (0.26-1.38) [174]	nd	Poor
Infection										4 (17%) [7 (30%)]	RR 0.57 (0.19-1.69) [175]	nd	Poor
Leukopenia										0 (0%) [2 (9%)]	--	nd	Poor
Severe infections	El-Shafey 2010[24] Egypt	6 mo (6 mo)	MMF	i.v. Cyc	24 (24)	23 (23)	S_{Cr} 132 µmol/l GFR 73.8 ml/min	1.98.g/d	Egyptian 100%	2 (8%) [2 (9%)]	RR 0.96 (0.15-6.25)[176]	nd	Good

[172] Calculated by ERT
[173] Calculated by ERT
[174] Calculated by ERT
[175] Calculated by ERT
[176] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
Leukopenia										4 (17%) [3 (13%)]	RR 1.28 (0.32-5.10)[177]		
Diarrhea										5 (21%) [2 (9%)]	RR 2.40 (0.52-11.14)[178]		

[177] Calculated by ERT
[178] Calculated by ERT

Supplementary table 73. Summary table of RCTs examining MMF vs. i.v. Cyc for induction therapy in patients with lupus nephritis (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results			*P* value	Quality
			Intervention	Control	Intervention	Control				Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria														
Proteinuria	Wang 2007[85] China	6 mo (6 mo)	MMF	i.v. Cyc	9 (9)	11 (11)	S_{Cr} 1.65 mg/dl	4.70 g/24h	nd	g/24h	4.7 (3.6)	1.35 (2.2)	0.001	Poor
Urine protein	Ginzler 2005[29] US	6 mo (6 mo)	MMF	i.v. Cyc	71 (71)	69 (69)	Scr 1.06 mg/dl	4.1 g/24h	Black 61% White 17% Hispanic 14% Asian 8%	g/24 h	4.1 (4.4)	2.03 (1.46)	nd	Fair
ΔProteinuria	Ong 2005[60] Malaysia	6 mo (6 mo)	MMF	i.v. Cyc	19 (26)	25 (28)	S_{Cr} 96.5 µmol/l GFR 97 ml/min	1.8 g/24h	Malaysian 42% Chinese 53% Indian 5%	g/24h	1.8 (3)	1.1 (1.9)	0.04	Fair
Proteinuria	El-Shafey 2010[24] Egypt	6 mo (6 mo)	MMF	i.v. Cyc	24 (24)	23 (23)	S_{Cr} 132 µmol/l GFR 73.8 ml/mi	1.98.g/d	Egyptian 100%	g/d	1.98 (2.09)	1.30 (1.37)	NS (0.82)	Good
S_{Cr}/GFR/CrCl														
S_{Cr}	Wang 2007[85] China	6 mo (6 mo)	MMF	i.v. Cyc	9 (9)	11 (11)	S_{Cr} 1.65 mg/dl	4.70 g/24h	nd	mg/dl	1.65 (0.94)	1.38 (0.85)	NS	Poor
S_{Cr}	Ginzler 2005[29] US	6 mo (6 mo)	MMF	i.v. Cyc	71 (71)	69 (69)	Scr 1.06 mg/dl	4.1 g/24h	Black 61% White 17% Hispanic 14% Asian 8%	mg/dl	1.06 (1.08)	0.91 (0.85)	nd	Fair
S_{Cr}	Ong 2005[60] Malaysia	6 mo (6 mo)	MMF	i.v. Cyc	19 (26)	25 (28)	S_{Cr} 96.5 µmol/l GFR 97 ml/min	1.8 g/d	Malaysian 42% Chinese 53% Indian 5%	µmol/l	96.5 (64)	109.5 (94.4)	NS	Fair
eGFR	El-Shafey 2010[24] Egypt	6 mo (6 mo)	MMF	i.v. Cyc	24 (24)	23 (23)	S_{Cr} 132 µmol/l GFR 73.8 ml/mi	1.98.g/d	Egyptian 100%	ml/min	73.8 (69.1)	29.4 (20.0)	NS (0.16)	Good

Supplementary table 74. Existing systematic review on Cyc vs. AZA for induction treatment in patients with lupus nephritis

Study, Year, RefID	Study Eligibility Criteria	Interventions (Studies)	Outcomes	Conclusions	Comments	Yes/No
Flanc 2004[26] **Date Base:** 1. Cochrane Central Register of Controlled Trials 2. Medline and preMedline 3. Embase **Search Dates**: CENTRAL - issue 2, 2003 1966 -2003 1980- 2003 N Studies: 25 N Subjects: 915	RCTs and quasi-RCTs comparing treatments for proliferative lupus nephritis in both adult and pediatric patients with biopsy proven Class III, IV, Vc, Vd lupus nephritis were included. All treatments were considered.	Trials with the following treatment options were considered: 1. corticosteroids - including prednisolone, prednisone and methyl-prednisolone 2. other immunosuppressive agents - including Azathioprine, cyclophosphamide, MMF and cyclosporine 3. plasma exchange or plasmapheresis; 4. Other agents (e.g. immunoglobulins). 5. Non-specific treatment options (e.g. antihypertensive agents)were not included in the present analysis as these do not specifically relate to LN but more broadly to preventing the progression of CKD	Dichotomous: 1. All cause mortality; 2. ESRD (need for RRT) 3. Doubling of Scr 4. Stable renal function - <20% worsening of Scr 5. Deterioration of renal function - >20% worsening of Scr 6. Relapse of LN. Toxicity: 1. major infection rate (all cause infection excluding HSV) 2. HSV infection 3. Ovarian failure 4. Bone toxicity (avascular necrosis or fracture) 5. bladder toxicity (haemorrhagic cystitis) 6. Development of malignancy. Remission of proteinuria according to the definitions of Chan 2000: complete remission: urinary protein excretion <0.3g/24 h. Continuous outcomes : 1. Scr (µmol/l) 2. CrCl (ml/min); 3. 24 h urinary protein excretion) (g/24 h);	Induction with Cyclophosphamide and steroids is probably an acceptable therapy as there is more data on cyclophosphamide as an induction agent. Lack of data on other agents and the lack of direct comparison of azathioprine to cyclophosphamide make it difficult to recommend other agents until further research becomes available. Given the risk of infertility, it is reasonable that the minimal effective cumulative dose of cyclophosphamide be used. It is not possible to be more specific about optimal dosing schedules. Based on this review plasma exchange cannot be recommended.	Is eligibility criteria similar to the guideline	Yes, included RCTs
					Are there any limitations to systematic review methodology	No
					Is limitation to evidence clearly addressed by the authors	Yes
Description of limitations of evidence by authors	Trial quality varied greatly amongst RCTs. The small size of many of the included trials causes this analysis to have small numbers overall. Subjects differed between studies. The severity of renal impairment and the proportion of patients with Class IV LN differed amongst trials. Whilst some RCTs had very long periods of follow-up, others were much shorter and inadequately powered to detect events.					

Author, Year, RefID	Intervention	Control	Outcome	N studies (N intervention group/ total N)	Pooled OR (95% CI)	*P*-value	Test for heterogeneity	
							I^2 Statistic	*P*-value
Flanc 2004[26] Study Years: 1966-2003	**Mortality**							
	Cyc	AZA	All cause mortality	1 (38/57)	0.79 [0.36, 1.70]	0.5	NA	NA
	ESRD/ Doubling of Scr							
	Cyc	AZA	ESRD	1 (38/57)	0.42 [0.15, 1.19]	0.1	NA	NA
			Doubling of Scr	1 (38/57)	0.56 [0.26, 1.22]	0.1		
			Stable renal function	1 (38/57)	1.32 [0.86, 2.01]	0.2		
			Deterioration of renal function	1 (20/30)	0.67 [0.18, 2.42]	0.5		
	Adverse events							
	Cyc	AZA	Major infection	1 (38/57)	1.25 [0.27, 5.86]	0.8	NA	NA
			Herpes Zoster	1 (38/57)	2.75 [0.68, 11.18]	0.2		
			Ovarian failure	1 (27/45)	3.33 [1.12, 9.88]	0.03		
			Bladder toxicity	1 (38/57)	3.59 [0.19, 66.14]	0.4		
			Malignancy	1 (38/57)	0.75 [0.14, 4.12]	0.7		

Supplementary table 75. Summary table of RCT examining Cyc vs. AZA for induction treatment in patients with lupus nephritis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
Mortality													
Death	Grootscholten 2006[30] Netherlands	6 y (2 y)	Cyc	AZA	50 (50)	37 (37)	S_{Cr} 112 µmol/l GFR 65 ml/min	4.3 g/24h	White 70%	2 (4%) [3 (8%)]	RR 0.49 (0.09-2.81)	NS (0.426)	Fair
ESRD/ Doubling of Scr													
ESRD	Grootscholten 2006[30] Netherlands	6 y (2 y)	Cyc	AZA	50 (50)	37 (37)	S_{Cr} 112 µmol/l GFR 65 ml/min	4.3 g/24h	White 70%	0 (0%) [1 (3%)]	--	nd	Fair
Doubling of S_{Cr}										2 (4%) [6 (16%)]	RR 0.25 (0.05–1.15)	NS (0.075)	
Remission													
Remission	Grootscholten 2006[30] Netherlands	2 y (2 y)	Cyc	AZA	50 (50)	37 (37)	S_{Cr} 112 µmol/l GFR 65 ml/min	4.3 g/24h	White 70%	*nd	nd	NS	Fair
Relapse													
Renal relapse	Grootscholten 2006[30] Netherlands	6 y (2 y)	Cyc	AZA	50 (50)	37 (37)	S_{Cr} 112 µmol/l GFR 65 ml/min	4.3 g/24h	White 70%	2 (4%) [10 (27%)]	RR 0.15 (0.03-0.64)	0.010	Fair
Adverse events													
Premature ovarian failure	Grootscholten 2006[30] Netherlands	6 y (2 y)	Cyc	AZA	50 (50)	37 (37)	S_{Cr} 112 µmol/l GFR 65 ml/min	4.3 g/24h	White 70%	2 (4%) [2 (5%)]	RR 0.74 (0.03-0.64)	NS (0.758)	Fair
Infection rate (events/100 patient y)		2 y (2 y)								18 [37]	--	nd	
Herpes zoster (events/100 patient y)										3 [12]	--	nd	
Hospital admission for infections										nd	RR 1.1 (0.6–2.0)	NS	

*Only Kaplan Meier curves showing cumulative incidence of partial and complete remission

Supplementary table 76. Summary table of RCT examining Cyc vs. AZA for induction treatment in patients with lupus nephritis (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results			*P* value	Quality
			Intervention	Control	Intervention	Control				Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria														
Proteinuria	Grootscholten 2006[30] Netherlands	6 y (2 y)	Cyc	AZA	50 (50)	37 (37)	S_{Cr} 112 µmol/l GFR 65 ml/min	4.3 g/24h	White 70%	g/24h	4.3 (3.2)	0.2 (0.4)	NS	Fair
S_{Cr}/GFR/CrCl														
S_{Cr}	Grootscholten 2006[30] Netherlands	6 y (2 y)	Cyc	AZA	50 (50)	37 (37)	S_{Cr} 112 µmol/l GFR 65 ml/min	4.3 g/24h	White 70%	µmol/l	112 (109)	80 (86)	NS	Fair

Supplementary table 77. Summary table of RCT examining low vs. high dose i.v. Cyc in patients with lupus nephritis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/ HR		
Mortality													
Death	Houssiau 2002[38], 2011[39] Europe	41 mo (3 mo low; 12 mo high)	Low dose Cyc	High dose Cyc	44 (44)	45 (46)	S_{Cr} 1.15 mg/dl	3.03 g/dl	Caucasian 84% Asian 7% Black 9%	2 (5%) [0 (0%)]	--	nd	Fair
		10 y follow-up								5 (12%) [2 (4%)]	RR 2.62 (0.54-12.77)[179]	nd	
ESRD/ doubling of S_{Cr}													
ESRD	Houssiau 2002[38], 2011[39] Europe	41 mo (High dose 12 mo Low dose 3 mo)	Low dose Cyc	High dose Cyc	44 (44)	45 (46)	S_{Cr} 1.15 mg/dl	3.03 g/dl	Caucasian 84% Asian 7% Black 9%	1 (2%) [2 (4%)]	RR 0.54 (0.05-5.70)[180]	nd	Fair
ESRD		73 mo (3 mo low; 12 mo high)								1 (2%) [3 (7%)]	HR 0.35 (0.04-3.37)	NS (0.34)	
Doubling of S_{Cr}		73 mo (3 mo low; 12 mo high)								7 (17%) [1 (2%)]	HR 2.2 (0.66-7.27)	NS (0.19)	
ESRD		10 y follow-up								2 (4%) [4 (9%)]	RR 0.52 (0.10-2.71)[181]	nd	
Sustained Doubling of S_{Cr}										6 (14%) [5 (12%)]	RR 1.26 (0.42-3.81)[182]		
Remission													
Renal remission	Houssiau 2002[38] Europe	41 mo (3 mo low; 12 mo high)	Low dose Cyc	High dose Cyc	44 (44)	45 (46)	S_{Cr} 1.15 mg/dl	3.03 g/dl	Caucasian 84% Asian 7% Black 9%	30 (71%) [22 (54%)]	HR 1.26 (0.72-2.21)	NS (0.36)	Fair
Adverse events													
Severe infection	Houssiau 2002[38], 2011[39] Europe	41 mo (3 mo low; 12 mo high)	Low dose Cyc	High dose Cyc	44 (44)	45 (46)	S_{Cr} 1.15 mg/dl	3.03 g/dl	Caucasian 84% Asian 7% Black 9%	7 (11%) [17 (22%)]	HR 0.5	NS (0.2)	Fair
Leukopenia										5 (11%) [5 (11%)]	RR 1.02 (0.32-3.29)[183]	nd	
Menopause										2 (4%) [2 (4%)]	RR 1.02 (0.15-6.94)[184]	nd	

[179] Calculated by ERT
[180] Calculated by ERT
[181] Calculated by ERT
[182] Calculated by ERT
[183] Calculated by ERT
[184] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/ HR		
Transient amenorrhea										1 (2%) [1 (2%)]	RR 1.02 (0.07-15.85)[185]	nd	
Cancers		10 y (3 mo low; 12 mo high)								6 (15%) [1 (2%)]	RR 6.29 (0.79-50.04)[186]	NS (0.10)	
Cardiac/arterial events										3 (7%) [4 (9%)]	RR 0.79 (0.19-3.30)[187]	NS	

[185] Calculated by ERT
[186] Calculated by ERT
[187] Calculated by ERT

Supplementary table 78. Existing systematic review on i.v. vs. p.o. Cyc treatment in patients with lupus nephritis

Study, Year, RefID	Study Eligibility Criteria	Interventions (Studies)	Outcomes	Conclusions	Comments	Yes/No
Flanc 2004[26] **Date Base:** 4. Cochrane Central Register of Controlled Trials 5. Medline and preMedline 6. Embase **Search Dates**: CENTRAL - issue 2, 2003 1966 -2003 1980- 2003 N Studies: 25 N Subjects: 915	RCTs and quasi-RCTs comparing treatments for proliferative lupus nephritis in both adult and pediatric patients with biopsy proven Class III, IV, Vc, Vd lupus nephritis were included. All treatments were considered.	Trials with the following treatment options were considered: 6. corticosteroids - including prednisolone, prednisone and methyl-prednisolone 7. other immunosuppressive agents - including Azathioprine, cyclophosphamide, MMF and cyclosporine 8. plasma exchange or plasmapheresis; 9. Other agents (e.g. immunoglobulins). 10. Non-specific treatment options (e.g. antihypertensive agents)were not included in the present analysis as these do not specifically relate to LN but more broadly to preventing the progression of CKD	Dichotomous: 7. All cause mortality; 8. ESRD (need for RRT) 9. Doubling of Scr 10. Stable renal function - <20% worsening of Scr 11. Deterioration of renal function - >20% worsening of Scr 12. Relapse of LN. Toxicity: 7. major infection rate (all cause infection excluding HSV) 8. HSV infection 9. Ovarian failure 10. Bone toxicity (avascular necrosis or fracture) 11. bladder toxicity (haemorrhagic cystitis) 12. Development of malignancy. Remission of proteinuria according to the definitions of Chan 2000: complete remission: urinary protein excretion <0.3g/24 h. Continuous outcomes : 4. Scr (µmol/l) 5. CrCl (ml/min); 6. 24 h urinary protein excretion) (g/24 h);	Induction with Cyclophosphamide and steroids is probably an acceptable therapy as there is more data on cyclophosphamide as an induction agent. Lack of data on other agents and the lack of direct comparison of azathioprine to cyclophosphamide make it difficult to recommend other agents until further research becomes available. Given the risk of infertility, it is reasonable that the minimal effective cumulative dose of cyclophosphamide be used. It is not possible to be more specific about optimal dosing schedules. Based on this review plasma exchange cannot be recommended.	Is eligibility criteria similar to the guideline	Yes, included RCTs
					Are there any limitations to systematic review methodology	No
					Is limitation to evidence clearly addressed by the authors	Yes
Description of limitations of evidence by authors	Trial quality varied greatly amongst RCTs. The small size of many of the included trials causes this analysis to have small numbers overall. Subjects differed between studies. The severity of renal impairment and the proportion of patients with Class IV LN differed amongst trials. Whilst some RCTs had very long periods of follow-up, others were much shorter and inadequately powered to detect events.					

Author, Year, RefID	Intervention	Control	Outcome	N studies (N intervention group/ total N)	Pooled OR[1](95% CI)	*P*-value	Test for heterogeneity	
							I^2 Statistic	*P*-value
Flanc, 2004[26] Study Years: 1966-2003	**Mortality**							
	i.v. Cyc	p.o. Cyc	All cause mortality	1 (20/38)	0.51 [0.18, 1.47]	0.2	NA	NA
	ESRD/ doubling of Scr							
	i.v. Cyc	p.o. Cyc	ESRD	1 (20/38)	0.23 [0.03, 1.83]	0.2	NA	NA
			Doubling of Scr	1 (20/38)	0.72 [0.23, 2.27	0.6	NA	NA
			Stable renal function	1 (20/38)	1.11 [0.77, 1.59]	0.6	NA	NA
			Deterioration of renal function	1 (20/38)	0.72 [0.23, 2.27]	0.6	NA	NA
	Adverse events							
	i.v. Cyc	p.o. Cyc	Major infection	1 (20/38)	0.60 [0.11, 3.19]	0.5	NA	NA
			Herpes Zoster	1 (20/38)	0.75 [0.28, 2.04]	0.6	NA	NA
			Ovarian failure	1 (17/27)	0.67 [0.35, 1.28]	0.2	NA	NA
			Bladder toxicity	1 (20/38)	0.13 [0.01, 2.34]	0.2	NA	A
			Malignancy	1 (20/38)	1.20 [0.31, 4.65]	0.8	NA	NA

Supplementary table 79. Summary table of RCT examining i.v. Cyc vs. p.o. Cyc in patients with lupus nephritis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
Mortality													
Death	Yee 2004[87] Europe	2 y (2 y)	i.v. Cyc	Daily p.o. Cyc + AZA	13 (13)	16 (16)	nd	nd	White 31% Asian 8% Afro Caribbean 0% Unknown 62%	2 (15%) [1 (6%)]	RR 2.46 (0.25-24.22) [188]	nd	Poor
RRT/ doubling of S_{Cr}													
Doubled S_{Cr}	Yee 2004[87] Europe	2 y (2 y)	i.v. Cyc	Daily p.o. Cyc + AZA	13 (13)	16 (16)	nd	nd	White 31% Asian 8% Afro Caribbean 0% Unknown 62%	0 (0%) [1 (6%)]	--	NS (0.49)	Poor
Dialysis										0 (0%) [2 (13%)]	--		Poor
Adverse Events													
Neutropenia	Yee 2004[87] Europe	2 y (2 y)	i.v. Cyc	Daily p.o. Cyc + AZA	13 (13)	16 (16)	nd	nd	White 31% Asian 8% Afro Caribbean 0% Unknown 62%	1 (8%) [3 (19%)]	RR 0.41 (0.05-3.49) [189]	nd	Poor
Nausea vomiting										3 (23%) [1 (6%)]	RR 3.69 (0.43-31.43) [190]	nd	Poor
Infections										5 (39%) [4 (25%)]	RR 1.54 (0.52-4.59) [191]	nd	Poor
Hemorrhagic cystitis										0 (0%) [1 (6%)]	--	nd	Poor
Malignancy										1 (8%) [0 (0%)]	--	nd	Poor
Permanent amenorrhea										1 (8%) [1 (6%)]	RR 1.23 (0.08-17.83) [192]	nd	Poor

[188] Calculated by ERT
[189] Calculated by ERT
[190] Calculated by ERT
[191] Calculated by ERT
[192] Calculated by ERT

Supplementary table 80. Summary table of RCT examining CsA vs. AZA for maintenance therapy in patients with lupus nephritis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
Renal flare												
Proteinuric flares	Moroni 2006[57] Italy	4 y (4 y)	Cyc	AZA	36 (36)	33 (33)	GFR 93 ml/min S_{Cr} 0.9 mg/dl	2.8 g/24h	4 (11%) [6 (18%)]	RR 0.61 (0.19-1.98)[193]	nd	Fair
Nephritic flare									1 (3%) [1 (3%)]	RR 0.92 (0.06-14.07)[194]	nd	
Undetectable proteinuria	Moroni 2006[57] Italy	4 y (4 y)	Cyc	AZA	36 (36)	33 (33)	GFR 93 ml/min S_{Cr} 0.9 mg/dl	2.8 g/24h	15 (42%) [5 (15%)]	RR 2.75 (1.12-6.73)[195]	0.045	Fair
Adverse events												
Leukopenia	Moroni 2006[57] Italy	4 y (4 y)	Cyc	AZA	36 (36)	33 (33)	GFR 93 ml/min S_{Cr} 0.9 mg/dl	2.8 g/24h	4 (11%) [10 (30%)]	RR 0.37 (0.13-1.06)[196]	nd	Fair
Infections									7 (19%) [14 (42%)]	RR 0.46 (0.21-0.99)[197]	nd	
Anemia									5 (14%) [5 (15%)]	RR 0.92 (0.29-2.88)[198]	nd	
Hypertension									7 (19%) [5 (15%)]	RR 1.28 (0.45-3.65)[199]	nd	
Hyperlipidemia									2 (6%) [4 (12%)]	RR 0.46 (0.09-2.34)[200]	nd	
Gum hyperplasia									2 (6%) [0 (0%)]	--	nd	
Hypertrichosis									2 (6%) [0 (0%)]	--	nd	

[193] Calculated by ERT
[194] Calculated by ERT
[195] Calculated by ERT
[196] Calculated by ERT
[197] Calculated by ERT
[198] Calculated by ERT
[199] Calculated by ERT
[200] Calculated by ERT

Diabetes	0 (0%) [1 (3%)]	--	nd
Hyperkalemia	1 (3%) [0 (0%)]	--	nd
Hypertensive crisis	1 (3%) [0 (0%)]	--	nd
Arthralgias	14 (39%) [3 (9%)]	RR 4.28 (1.35-13.56)[201]	nd
GI disorders	11 (31%) [3 (9%)]	RR 3.36 (1.03-11.00)[202]	nd

[201] Calculated by ERT
[202] Calculated by ERT

Supplementary table 81. Summary table of RCT examining CsA vs. AZA for maintenance therapy in patients with lupus nephritis (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
ΔProteinuria	Moroni 2006[57] Italy	2 y (2 y)	Cyc	AZA	36 (36)	33 (33)	GFR 93 ml/min S_{Cr} 0.9 mg/dl	2.8 g/24h	g/d	2.8 (2.2)	0.38 (0.53)	NS	Poor
		4 y (4 y)								2.8 (2.2)	0.23 (0.33)		
S_{Cr}/GFR/CrCl													
ΔCrCl	Moroni 2006[57] Italy	2 y (2 y)	Cyc	AZA	36 (36)	33 (33)	GFR 93 ml/min S_{Cr} 0.9 mg/dl	2.8 g/24h	ml/min	92.5 (104.1)	82.6 (09.9)	0.044	Poor
		4 y (4 y)								92.5 (104.1)	-6.9 (-5.1)	NS	

Supplementary table 82. Summary table of RCT examining i.v. Cyc vs. prednisone in patients with membranous lupus nephritis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
Remission													
Remission	Austin 2009[4] US	12 mo (12 mo)	Cyc	Prednisone	15 (15)	15 (15)	GFR 83 ml/min/1.73m^2	5.4 g/d	Black 64% White 29% Hispanic 7%	9 (60%) [4 (27%)]	RR 2.25 (0.88-5.73)[203]	0.04	Fair
Complete remission										6 (40%) [2 (13%)]	RR 3.00 (0.72-12.55) [204]	nd	Fair
ESRD/ doubling of S_{Cr}													
Doubling of S_{Cr}	Austin 2009[4] US	12 mo (12 mo)	Cyc	Prednisone	15 (15)	15 (15)	GFR 83 ml/min/1.73m^2	5.4 g/d	Black 64% White 29% Hispanic 7%	1 (8%) [2 (13%)]	RR 0.50 (0.05-4.94) [205]	nd	Fair
Adverse Events													
Leukopenia	Austin 2009[4] US	12 mo (12 mo)	Cyc	Prednisone	15 (15)	15 (15)	GFR 83 ml/min/1.73m^2	5.4 g/d	Black 64% White 29% Hispanic 7%	0 (0%) [0 (0%)]	--	nd	Fair
Amenorrhea										0 (0%) [0 (0%)]	--	nd	Fair
Nausea/anorexia										2 (17%) [0 (0%)]	--	nd	Fair
↑BP with or without ↑S_{Cr}										9 (75%) [0 (0%)]	--	nd	Fair
Gingival hyperplasia/ ↑facial hair										8 (67%) [0 (0%)]	--	nd	Fair
Paresthesia/ tremor										4 (33%) [0 (0%)]	--	nd	Fair
Infections										7 (58%) [4 (27%)]	RR 1.75 (0.64-4.75) [206]	nd	Fair
Pneumonia										2 (17%) [1 (7%)]	RR 2.00 (0.20-19.78) [207]	nd	Fair
Herpes zoster										0 (0%) [0 (0%)]	--	nd	Fair

[203] Calculated by ERT
[204] Calculated by ERT
[205] Calculated by ERT
[206] Calculated by ERT
[207] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
Other										5 (42%) [3 (20%)]	RR 1.67 (0.48-5.76) [208]	nd	Fair
Osteoporosis/ hip avascular necrosis										2 (17%) [4 (27%)]	RR 0.50 (0.11-2.33) [209]	nd	Fair
Basal cell skin cancer										0 (0%) [0 (0%)]	--	nd	Fair

[208] Calculated by ERT
[209] Calculated by ERT

Supplementary table 83. Summary table of RCT examining i.v. CsA vs. prednisone in patients with membranous lupus nephritis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
Remission													
Remission	Austin 2009[4] US	12 mo (12 mo)	CsA	Prednisone	12 (12)	15 (15)	GFR 83 ml/min/1.73m^2	5.4 g/d	Black 64% White 29% Hispanic 7%	10 (83%) [4 (27%)]	RR 3.13 (1.30-7.51) [210]	0.002	Fair
Complete remission										6 (50%) [2 (13%)]	RR 3.75 (0.92-15.34) [211]	nd	Fair
ESRD/ doubling of S_{Cr}													
Doubling of S_{Cr}	Austin 2009[4] US	12 mo (12 mo)	CsA	Prednisone	12 (12)	15 (15)	GFR 83 ml/min/1.73m^2	5.4 g/d	Black 64% White 29% Hispanic 7%	1 (7%) [2 {13%)]	RR 0.63 (0.06-6.09) [212]	nd	Fair
Adverse Events													
Leukopenia	Austin 2009[4] US	12 mo (12 mo)	CsA	Prednisone	12 (12)	15 (15)	GFR 83 ml/min/1.73m^2	5.4 g/d	Black 64% White 29% Hispanic 7%	2 (13%) [0 (0%)]	--	nd	Fair
Amenorrhea										0.25 (25%) [0 (0%)]	--	nd	Fair
Nausea/anorexia										3 (20%) [0 (0%)]	--	nd	Fair
Infections										10 (67%) [4 (27%)]	RR 3.13 (1.30-7.51) [213]	nd	Fair
Pneumonia										0 (0%) [1 (7%)]	--	nd	Fair
Herpes zoster										2 (13%) [0 (0%)]	--	nd	Fair
Other										8 (53%) [3 (20%)]	RR 3.33 (1.12-9.90) [214]	nd	Fair
Osteoporosis/ hip avascular necrosis										3 (20%) [4 (27%)]	RR 0.94 (0.26-3.41) [215]	nd	Fair

[210] Calculated by ERT
[211] Calculated by ERT
[212] Calculated by ERT
[213] Calculated by ERT
[214] Calculated by ERT
[215] Calculated by ERT

Basal cell skin cancer			1 (7%) [0 (0%)]	--	nd	Fair

Supplementary table 84. Summary table of RCT CsA vs. i.v. Cyc in patients with membranous lupus nephritis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
Remission													
Remission	Austin 2009[4] US	12 mo (12 mo)	CsA	Prednisone	12 (12)	15 (15)	GFR 83 ml/min/1.73m^2	5.4 g/d	Black 64% White 29% Hispanic 7%	10 (83%) [9 (60%)]	RR 1.39 (0.86-2.25)[216]	nd	Fair
Complete remission										6 (50%) [6 (40%)]	RR 1.25 (0.54-2.89) [217]	nd	Fair
ESRD/ doubling of S_{Cr}													
Doubling of S_{Cr}	Austin 2009[4] US	12 mo (12 mo)	CsA	Prednisone	12 (12)	15 (15)	GFR 83 ml/min/1.73m^2	5.4 g/d	Black 64% White 29% Hispanic 7%	1 (7%) [1 (8%)]	RR 1.25 (0.09-17.98) [218]	nd	Fair
Relapse													
Incidence of relapse/100 patient mo	Austin 2009[4] US	12 mo (12 mo)	CsA	Prednisone	12 (12)	15 (15)	GFR 83 ml/min/1.73m^2	5.4 g/d	Black 64% White 29% Hispanic 7%	2 [0.2]	--	0.02	Fair
Adverse Events													
Leukopenia	Austin 2009[4] US	12 mo (12 mo)	CsA	Prednisone	12 (12)	15 (15)	GFR 83 ml/min/1.73m^2	5.4 g/d	Black 64% White 29% Hispanic 7%	0 (0%) [2 (13%)]	--	nd	Fair
Amenorrhea										0 (0%) (1/4 (25%)]	--	nd	Fair
Nausea/anorexia										2 (17%) [3 (20%)]	RR 0.83 (0.16-4.21) [219]	nd	Fair
↑BP with/without ↑S_{Cr}										9 (75%) [0 (0%)]	--	nd	Fair
Gingival hyperplasia/ ↑facial hair										8 (67%) [0 (0%)]	--	nd	Fair
Paresthesia/ tremor										4 (33%) [0 (0%)]	--	nd	Fair
Infections										7 (58%) [10 (67%)]	RR 0.88 (0.48-1.59) [220]	nd	Fair

[216] Calculated by ERT
[217] Calculated by ERT
[218] Calculated by ERT
[219] Calculated by ERT
[220] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
Pneumonia										2 (17%) [0 (0%)]	--	nd	Fair
Herpes zoster										0 (0%]) [2 (13%)]	--	nd	Fair
Other										5 (42%) [8 (53%)]	RR 0.78 (0.34-1.77) [221]	nd	Fair
Osteoporosis/hip avascular necrosis										2 (17%) [3 (20%)]	RR 0.83 (0.16-4.21) [222]	nd	Fair
Basal cell skin cancer										0 (0%) [1 (7%)]	--	nd	Fair

[221] Calculated by ERT
[222] Calculated by ERT

Supplementary table 85. Summary table of RCT examining rituximab + cyclophosphamide vs. rituximab in patients with proliferative lupus nephritis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
Remission												
Complete response	Li 2009[49] Hong Kong	48 wk (48 wk)	Rituximab + Cyc	Rituximab	10 (10)	9 (9)	S_{Cr} 134.8 µmol/l	3.8 g/24h	2 (20%) [2 (22%)]	RR 0.90 (0.16-5.13) [223]	nd	Poor
Partial response									5 (50%) [6 (66%)]	RR 0.75 (0.35-1.62) [224]	nd	Poor
Complete or partial response									7 (70%) [8 (88%)]	RR 0.79 (0.49-1.26) [225]	nd	Poor
Total sustained complete response									4 (21%)	--	nd	Poor
Adverse events												
AE- Infections	Li 2009[49] Hong Kong	48 wk (48 wk)	Rituximab + Cyc	Rituximab	10 (10)	9 (9)	S_{Cr} 134.8 µmol/l	3.8 g/24h	5 (50%) [7 (77%)]	RR 0.64 (0.32-1.31) [226]	nd	Fair
AE-Cramps									0 (0%) [4 (44%)]	--	nd	Fair
AE-Ankle swelling									4 (40%) [3 (33%)]	RR 1.20 (0.36-3.97) [227]	nd	Fair
AE-Insomnia									2 (20%) [0 (0%)]	--	nd	Fair
AE-Pruritis									2 (20%) [0 (0%)]	--	nd	Fair
AE-Dyspepsia									2 (20%) [0 (0%)]	--	nd	Fair
AE-Urticaria									2 (20%) [0 (0%)]	--	nd	Fair
AE-Chest pain									1 (10%) [0 (0%)]	--	nd	Fair
AE-Abdominal distension									1 (10%) [0 (0%)]	--	nd	Fair
AE-Depression									0 (0%) [1 (11%)]	--	nd	Fair
AE-Malaise									1 (10%) [0 (0%)]	--	nd	Fair

[223] Calculated by ERT
[224] Calculated by ERT
[225] Calculated by ERT
[226] Calculated by ERT
[227] Calculated by ERT

Supplementary table 86. Summary table of RCT examining rituximab + cyclophosphamide vs. rituximab in patients with proliferative lupus nephritis (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
Proteinuria	Li 2009[49] Hong Kong	48 wk (48 wk)	Rituximab + Cyclophosphamide	Rituximab	10 (10)	9 (9)	S_{Cr} 134.8 µmol/l	3.8 g/24h	g/24h	3.8 (4.1)	nd (nd)	NS	Poor
S_{Cr}/GFR/CrCl													
CrCl	Li 2009[49] Hong Kong	48 wk (48 wk)	Rituximab + Cyclophosphamide	Rituximab	10 (10)	9 (9)	S_{Cr} 134.8 µmol/l	3.8 g/24h	µmol/l	64.2 (81.4)	nd (nd)	NS	Poor

Supplementary table 87. Summary table of RCT examining TAC vs. placebo in patients with lupus nephritis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
Proteinuria												
Daily UPE <0.3 g/24h	Miyasaka 2009[56] Japan	28 wk (28 wk)	Tacrolimus	Placebo	27 (28)	33 (35)	GFR 101 ml/min S_{Cr} 0.67 mg/dl	1.6 g/d	4 (15%) [1 (3%)]	RR 4.89 (0.58-41.20) [228]	NS	Fair
Kidney function												
Maintenance of normal S_{Cr}	Miyasaka 2009[56] Japan	28 wk (28 wk)	Tacrolimus	Placebo	27 (28)	33 (35)	GFR 101 ml/min S_{Cr} 0.67 mg/dl	1.6 g/d	22 (92%) [26 (90%)]	RR 1.03 (0.80-1.33) [229]	NS	Fair
Adverse events												
All infections	Miyasaka 2009[56] Japan	28 wk (28 wk)	Tacrolimus	Placebo	27 (28)	33 (35)	GFR 101 ml/min S_{Cr} 0.67 mg/dl	1.6 g/d	16 (57%) [20 (57%)]	RR 0.86 (0.59-1.26) [230]	NS	Fair
Serious infections									2 (7%) [1 (3%)]	RR 2.15 (0.21-22.37) [231]	NS	
Hyperlipidemia									2 (7%) [3 (9%)]	RR 0.72 (0.13-3.96) [232]	NS	
↑Blood glucose									4 (14%) [0 (0%)]	--	<0.05	
↑HbA1c									2 (7%) [0 (0%)]	--	NS	
Nausea									4 (14%) [0 (0%)]	--	<0.05	
Hypertension									2 (7%) [3 (9%)]	RR 0.72 (0.13-3.96) [233]	NS	

[228] Calculated by ERT
[229] Calculated by ERT
[230] Calculated by ERT
[231] Calculated by ERT
[232] Calculated by ERT
[233] Calculated by ERT

Supplementary table 88. Summary table of RCT examining TAC vs. placebo in patients with lupus nephritis (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
S_{Cr}/GFR/CrCl													
CrCl	Miyasaka 2009[56] Japan	12 wk (28 wk) 28 wk (28 wk)	Tacrolimus	Placebo	27 (28)	33 (35)	GFR 101 ml/min S_{Cr} 0.67 mg/dl	1.6 g/d	ml/min	101.4 [95.8]	79.1 [93.4] 78.2 [92.9]	0.005 0.060	Fair
Disease activity													
Lupus nephritis disease activity index	Miyasaka 2009[56] Japan	28 wk (28 wk)	Tacrolimus	Placebo	27 (28)	33 (35)	GFR 101 ml/min S_{Cr} 0.67 mg/dl	1.6 g/d	nd	5.3 [5.2]	-1.8 [0.0]	<0.001	Fair

Supplementary table 89. Summary table of a study examining TAC vs. standard protocols of steroid + p.o. Cyc or AZA in patients with class V lupus (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
Remission												
Complete remission	Szeto 2008[77] China	12 wk (6 mo)	TAC	Standard protocols of steroid + p.o. Cyc or AZA	18 (18)	19 (19)	S_{Cr} 93 mg/dl GFR 103 ml/min	4.57 g/d	28% [16%]	--	NS (0.5)	Poor
Partial remission									50% [47%]	--	NS (0.5)	
Complete remission		24 wk (6 mo)							39% [37%]	--	NS (0.5)	Poor
Partial remission									44% [58%]	--	NS (0.5)	
Adverse events												
Infection	Szeto 2008[77] China	12 wk (6 mo)	TAC	Standard protocols of steroid + p.o. Cyc or AZA	18 (18)	19 (19)	S_{Cr} 93 mg/dl GFR 103 ml/min	4.57 g/d	3 (17%) [2 (11%)]	RR 1.58 (0.30-8.40) [234]	nd	Poor
Elevated LFTs									1 (6%) [1 (6%)]	RR 1.06 (0.07-15.64) [235]	nd	
Angioedema									1 (6%) [0 (0%)]	--	nd	
Tremor									2 (11%) [0 (0%)]	--	nd	
Dyspepsia									8 (44%) [0 (0%)]	--	nd	

[234] Calculated by ERT
[235] Calculated by ERT

Supplementary table 90. Summary table of a study examining TAC vs. standard protocols of steroid + p.o. Cyc or AZA in patients with class V lupus (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria													
ΔProteinuria	Szeto 2008[77] China	12 wk (6 mo)	TAC	Standard protocols of steroid + p.o. Cyc or AZA	18 (18)	19 (19)	S_{Cr} 93 mg/dl GFR 103 ml/min	4.57 g/d	g/d	4.57 (3.62)	76% (47%)	0.03	Poor
S_{Cr}/GFR/CrCl													
ΔeGFR	Szeto 2008[77] China	12 wk (6 mo)	TAC	Standard protocols of steroid + p.o. Cyc or AZA	18 (18)	19 (19)	S_{Cr} 93 mg/dl GFR 103 ml/min	4.57 g/d	ml/min/1.73m^2	102.8 (103.1)	nd	NS (0.7)	Poor

Supplementary table 91. Summary table of a study examining AZA vs. i.v. Cyc maintenance therapy in patients with lupus nephritis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				No. Events (%) Intervention [Control]	RR/OR/HR		
Mortality													
Mortality	Contreras 2004[15] 2005[16] US	30 mo (30 mo)	AZA + steroids	i.v. Cyc + steroids	19 (19)	20 (20)	S_{Cr} 1.7 mg/dl	5.7 mg/mg	Black 47% Hispanic 42% White 11%	0 (0)% [4 (20%)]	--	0.02	Fair
Cumulative rate of renal survival										80% [74%]	--	nd	Fair
Event-free survival for composite end point of death or chronic renal failure[236]		60-72 mo (30 mo)								nd 89% [80%]	--	0.009 nd	Fair
Relapse free survival		30 mo (30 mo)								nd	--	NS (0.12)	Fair
ESRD/ doubling of S_{Cr}													
Chronic renal failure[237]	Contreras 2004[15] 2005[16] US	30 mo (30 mo)	AZA + steroids	i.v. Cyc + steroids	19 (19)	20 (20)	S_{Cr} 1.7 mg/dl	5.7 mg/mg	Black 47% Hispanic 42% White 11%	1 (5)% [3 (15%)]	RR 0.35 (0.04-3.09) [238]	nd	Fair
Relapse													
Relapse	Contreras 2004[15] 2005[16] US	30 mo (30 mo)	AZA + steroids	i.v. Cyc + steroids	19 (19)	20 (20)	S_{Cr} 1.7 mg/dl	5.7 mg/mg	Black 47% Hispanic 42% White 11%	6 (32%) [8 (40%)]	RR 0.79 (0.34-1.85) [239]	nd	Fair
Adverse events													
Infection	Contreras 2004[15] 2005[16] US	30 mo (30 mo)	AZA + steroids	i.v. Cyc + steroids	19 (19)	20 (20)	S_{Cr} 1.7 mg/dl	5.7 mg/mg	Black 47% Hispanic 42% White 11%	29% [77%]	--	0.002	Fair
Amenorrhea										8% [32%]	--	0.03	Fair
Leukopenia										6% [10%]	--	0.43	Fair

[236] ESRD, transplant or doubling of S_{Cr} from lowest value achieved during induction
[237] ESRD, transplant or doubling of S_{Cr} from lowest value achieved during induction
[238] Calculated by ERT
[239] Calculated by ERT

Supplementary table 92. Summary table of a study examining MMF vs. i.v. Cyc maintenance therapy in patients with lupus nephritis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				No. Events (%) Intervention [Control]	RR/OR/HR		
Mortality													
Mortality	Contreras 2004[15] 2005[16] US	29 mo (29 mo)	MMF	i.v. Cyc + steroids	20 (20)	20 (20)	S_{Cr} 1.6 mg/dl	4.7 mg/mg	Black 45% Hispanic 50% White 5%	1 (5%) [4 (20%)]	RR 0.25 (0.03-2.05) [240]	NS (0.11)	Fair
Cumulative rate of renal survival										95% [74%]	--	nd	Fair
Event-free survival for composite end point of death or chronic renal failure[241]		29 mo (29 mo)								nd	--	0.005	Fair
		60-72 mo (29 mo)								89% [45%]		nd	
Relapse free survival		29 mo (29 mo)								nd	--	0.02	Fair
ESRD/ doubling of S_{Cr}													
Chronic renal failure[242]	Contreras 2004[15] 2005[16] US	29 mo (29 mo)	MMF	i.v. Cyc + steroids	20 (20)	20 (20)	S_{Cr} 1.6 mg/dl	4.7 mg/mg	Black 45% Hispanic 50% White 5%	1 (5)% [3 (15%)]	RR 0.33 (0.04-2.94) [243]	nd	Fair
Relapse													
Relapse	Contreras 2004[15] 2005[16] US	29 mo (29 mo)	MMF	i.v. Cyc + steroids	20 (20)	20 (20)	S_{Cr} 1.6 mg/dl	4.7 mg/mg	Black 45% Hispanic 50% White 5%	3 (15%) [8 (40%)]	RR 0.38 (0.12-1.21) [244]	nd	Fair
Adverse events													
Infection	Contreras 2004[15] 2005[16] US	29 mo (29 mo)	MMF	i.v. Cyc + steroids	20 (20)	20 (20)	S_{Cr} 1.6 mg/dl	4.7 mg/mg	Black 45% Hispanic 50% White 5%	32% [77%]		0.005	Fair
Amenorrhea										6% [32%]		0.03	Fair
Leukopenia										2% [10%]		NS (0.15)	Fair

[240] Calculated by ERT
[241] ESRD, transplant or doubling of S_{Cr} from lowest value achieved during induction
[242] ESRD, transplant or doubling of S_{Cr} from lowest value achieved during induction
[243] Calculated by ERT
[244] Calculated by ERT

Supplementary table 93. Evidence profile of studies examining MMF vs. AZA maintenance therapy in patients with lupus nephritis

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	3 RCTs (High)	156 (94)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Low	No difference	Critical
ESRD	1 RCT (High)	105 (53)	No limitations (0)	N/A	Direct (0)	Imprecision (-1) Sparse (-1)	Low	No difference	Critical
Remission	0 RCTs	--	--	--	--	--	--	--	High
Relapse	3 RCTs (High)	206 (105)	No limitations (0)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Moderate	No difference	High
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Kidney function (categorical)	1 RCT (High)	105 (53)	No limitations (0)	N/A	Direct (0)	Imprecision (-1) Sparse (-1)	Low	No difference	High
Proteinuria (continuous)	1 RCT (High)	62 (32)	Some limitations (-1)	N/A	Direct (0)	Sparse (-1)	Low	No difference	Moderate
Kidney function (continuous)	1 RCT (High)	62 (32)	Some limitations (-1)	N/A	Direct (0)	Sparse (-1)	Low	No difference	Moderate
Adverse events	3 RCTs (High)	206 (105)						No difference	Moderate

Balance of potential benefits and harm:
No difference

Quality of overall evidence:
Low

Supplementary table 94. Summary table of studies examining MMF vs. AZA maintenance therapy in patients with lupus nephritis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				No. Events (%) Intervention [Control]	RR/OR/HR		
Mortality													
Mortality	Contreras 2004[15] 2005[16] US	30 mo (30 mo)	MMF	AZA	20 (20)	19 (19)	S_{Cr} 1.7 mg/dl	4.7 mg/mg	Black 45% Hispanic 50% White 5%	1 (5%) [0 (0%)]	--	NS (0.33)	Fair
Cumulative rate of renal survival										95% [80%]	--	nd	Fair
Event-free survival for composite end point of death or chronic renal failure[245]		30 mo (30 mo)								--	--	NS (0.50)	Fair
		60-72 mo (30 mo)								89% [80%]		nd	
Relapse free survival		30 mo (30 mo)								--	--	NS (0.22)	Fair
Death	Chan 2000[10] China	12 mo (12 mo)	MMF+ prednisone	i.v. Cyc + prednisone, then AZA + prednisone	21 (21)	21 (21)	GFR 86 ml/min S_{Cr} 1.2 mg/dl	5.8 g/24h	nd	0 (0%) [2 (10%)]	--	NS (0.49)	Fair
Death/ESRD	Chan 2005[12] China	63 mo (≥12 mo)	MMF+ prednisone	i.v. Cyc + prednisone, then AZA + prednisone	32 (33)	30 (33)	GFR 72 ml/min S_{Cr} 1.28 mg/dl	5.32 g/24h	nd	0 (0%) [4 (12%)]	--	NS (0.062)	Fair
Death	Houssiau 2010[37] Europe	48 mo (44 mo)	MMF	AZA	53 (53)	52 (52)	S_{Cr} 1.01 mg/dl	3.63 g/24h	White 42% Black 6% Asian 5%	2 (4%) [0 (0%)]	--	nd	Good
ESRD/ doubling of S_{Cr}													
Chronic renal failure[246]	Contreras 2004[15] 2005[16] US	30 mo (30 mo)	MMF	AZA	20 (20)	19 (19)	S_{Cr} 1.7 mg/dl	4.7 mg/mg	Black 45% Hispanic 50% White 5%	1 (5)% [1 (5%)]	RR 0.95 (0.06-14.13) [247]	nd	Fair
Doubling S_{Cr}	Houssiau 2010[37] Europe	48 mo (44 mo)	MMF	AZA	53 (53)	52 (52)	S_{Cr} 1.01 mg/dl	3.63 g/24h	White 42% Black 6% Asian 5%	3 (6%) [4 (8%)]	RR 0.74 (0.17-3.13)[248]	nd	Good

[245] ESRD, transplant or doubling of S_{Cr} from lowest value achieved during induction
[246] ESRD, transplant or doubling of S_{Cr} from lowest value achieved during induction
[247] Calculated by ERT
[248] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				No. Events (%) Intervention [Control]	RR/OR/HR		
ESRD										1 (2%) 1 (2%)	RR 0.98 (0.06-15.28)[249]		
Relapse													
Relapse	Contreras 2004[15] 2005[16] US	30 mo (30 mo)	MMF	AZA	20 (20)	19 (19)	S_{Cr} 1.7 mg/dl	4.7 mg/mg	Black 45% Hispanic 50% White 5%	3 (15%) [6 (32%)]	RR 0.48 (0.14-1.63) [250]	nd	Fair
Relapse	Chan 2000[10] China	12 mo (12 mo)	MMF+ prednisone	i.v. Cyc + prednisone, then AZA + prednisone	21 (21)	21 (21)	GFR 86 ml/min S_{Cr} 1.2 mg/dl	5.8 g/24h	nd	3 (15%) [2 (11%)]	RR 1.50 (0.28-8.08) [251]	NS (0.15)	Fair
Time to relapse, wk										40 [39]	--	NS (0.70	
Relapse	Chan 2005[12] China	63 mo (≥12 mo)	MMF+ prednisone	i.v. Cyc + prednisone, then AZA + prednisone	32 (33)	30 (33)	GFR 72 ml/min S_{Cr} 1.28 mg/dl	5.32 g/24h	nd	11 (34%) [9 (30%)]	HR 1.536 (0.634-3.722)	NS (0.342)	Fair
Time to relapse, wk										20 [33]	--	nd	
Renal flare	Houssiau 2010[37] Europe	48 mo (44 mo)	MMF	AZA	53 (53)	52 (52)	S_{Cr} 1.01 mg/d	3.63 g/24h	White 42% Black 6% Asian 5%	10 (19%) 13 (25%)	HR 0.75 (0.33-1.71)	0.49	Good
Adverse events													
Infection	Contreras 2004[15] 2005[16] US	30 mo (30 mo)	MMF	AZA	20 (20)	19 (19)	1.7±1.6 mg/dl	4.7±4.3 mg/mg	Black 45% Hispanic 50% White 5%	32% [29%]	--	NS	Fait
Amenorrhea										6% [8%]	--	NS	
Leukopenia										2% [6%]	--	NS	
Infection	Chan 2000[10] China	12 mo (12 mo)	MMF+ prednisone	i.v. Cyc + prednisone, then AZA + prednisone	21 (21)	21 (21)	GFR 86 ml/min S_{Cr} 1.2 mg/dl	5.8 g/24h	nd	4 (19%) [7 (33%)]	RR 0.57 (0.20-1.66) [252]	NS (0.29)	Fair
Hair loss										0 (0%) [4 (19%)]	--	NS (0.11)	
Permanent amenorrhea										0 (0%) [1 (8%)]	--	NS (0.46)	

[249] Calculated by ERT
[250] Calculated by ERT
[251] Calculated by ERT
[252] Calculated by ERT

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				No. Events (%) Intervention [Control]	RR/OR/HR		
Leukopenia										0 (0%) [2 (10%)]	--	NS (0.49)	
Diarrhea										1 (5%) [0 (0%)]	--	NS (1.00)	
Incidence of infection	Chan 2005[12] China	63 mo (≥12 mo)	MMF+ prednisone	i.v. Cyc + prednisone, then AZA + prednisone	32 (33)	30 (33)	GFR 72 ml/min S_{Cr} 1.28 mg/dl	5.32 g/24h	nd	1/234 pt-mo [1/102.5 pt-mo]	Rate Ratio 2.28 (0.96-5.43)	NS (0.062)	Fair
Incidence of hospitalized infections										1/327.6 pt.mo [1/177 pt-mo]	Rate Ratio 1.85 (0.64-5.33)	NS (0.254)	
Hair loss										0 (0%) [9 (29%)]	--	nd	
Amenorrhea										4% [36%]	--	0.004	
Permanent amenorrhea										0% [56%]	--	nd	
Leukopenia										0 (0%) [8 (26%)]	--	nd	
GI upset										3 (9%) [1 (3%)]	RR 2.81 (0.31-25.58) [253]	nd	
Infection	Houssiau 2010[37] Europe	48 mo (44 mo)	MMF	AZA	53 (53)	52 (52)	S_{Cr} 1.01 mg/dl	3.63 g/24h	White 42% Black 6% Asian 5%	21 (40%) [14 (27%)]	RR 1.47 (0.84-2.57)[254]	nd	Good
Leukopenia										2 (4%) [11 (21%)]	RR 0.18 (0.04-0.77)[255]	nd	
Diarrhea										8 (15%) [8 (15%)]	RR 0.98 (0.40-2.42)[256]	nd	

[253] Calculated by ERT
[254] Calculated by ERT
[255] Calculated by ERT
[256] Calculated by ERT

Supplementary table 95. Summary table of studies examining MMF vs. AZA maintenance therapy in patients with lupus nephritis (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Race	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Baseline Intervention (Control)	Δ Intervention (Control)		
Scr/GFR													
S_{Cr}, mg/dl	Chan 2000[10] China	12 mo (12 mo)	MMF+ prednisone	i.v. Cyc + prednisone, then AZA + prednisone	21 (21)	21 (21)	GFR 86 ml/min S_{Cr} 1.2 mg/dl	5.8 g/24h	nd	1.13 (1.10)	-0.16 (-0.11)	NS	Fair
Cr Cl, ml/min/1.73 m^2										86 (77)	+6 (+5)	nd	Fair
S_{Cr} slope	Chan 2005[12] China	63 mo (≥12 mo)	MMF+ prednisone	i.v. Cyc + prednisone, then AZA + prednisone	32 (33)	30 (33)	GFR 72 ml/min S_{Cr} 1.28 mg/dl	5.32 g/24h	nd	1.27 (1.28)	-0.308 (0.242)	NS (0.914)	Fair
CrCl slope										67.4 (74.9)	0.142 (0.057)	NS (0.131)	Fair
Proteinuria													
Proteinuria	Chan 2000[10] China	12 mo (12 mo)	MMF+ prednisone	i.v. Cyc + prednisone, then AZA + prednisone	21 (21)	21 (21)	GFR 86 ml/min S_{Cr} 1.2 mg/dl	5.8 g/24h	nd	5.8 (3.7)	-5.3 (-3.5)	nd	Fair
Proteinuria-slope	Chan 2005[12] China	63 mo (≥12 mo)	MMF+ prednisone	i.v. Cyc + prednisone, then AZA + prednisone	32 (33)	30 (33)	GFR 72 ml/min S_{Cr} 1.28 mg/dl	5.32 g/24h	nd	6.21 (4.44)	-0.085 (-0.055)	NS (0.075)	Fair

Supplementary table 96. Evidence profile of i.v. vs. p.o. Cyc for ANCA vasculitis

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	1 RCT (High) 1 SR (3 RCTs)	149 (76) 129 (61)	Some limitations (-1) Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None	Moderate	No difference for mortality	Critical
RRT	1 RCT (High) 1 SR (3 RCTs)	149 (76) 129 (61)	Some limitations (-1) Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None	Moderate	No difference for RRT	Critical
Remission	1 RCT (High) 1 SR (3 RCTs)	149 (76) 97 (49)	Some limitations (-1) Some limitations (-1)	Important inconsistencies (-1)	Direct (0)	None	Low	No difference for i.v. cyclophosphamide	High
Relapse	1 RCT (High) 1 SR (3 RCTs)	149 (76) 119 (57))	Some limitations (-1) Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None	Moderate	Benefit for oral cyclophosphamide	High
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Kidney function (categorical)	0 RCTs	--	--	--	--	--	--	--	High
ΔProteinuria (continuous)	0 RCTs	--	--	--	--	--	--	--	Moderate
ΔKidney function (continuous)	1 RCT (High) 1 SR (2 RCT s)	149 (76) 52 (21)	Some limitations (-1) Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None	Moderate	No difference for change in kidney function	Moderate
Adverse events	1 RCT (High) 1 SR (3 RCTs)	149 (76) 129 (61)						Lower incidence of leukopenia with pulse cyclophosphamide	

Balance of potential benefits and harm:
Benefit for oral cyclophosphamide in preventing relapse

Quality of overall evidence:
Moderate

Supplementary table 97. Existing systematic review of Induction with pulse Cyc vs. daily p.o. Cyc in patients with ANCA vasculitis

Study, Year, RefID	Study Eligibility Criteria	Interventions (Studies)	Outcomes	Conclusions	Comments	Yes/No
Walters 2008[84] Date Base: 1. Cochrane Central Register of Controlled Trials 2. Cochrane Renal Group Specialized Register, 3. MEDLINE EMBASE Search Dates: 1966-2008 N Studies: 13 N Subjects: 702	All 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) looking at any intervention used for the treatment of renal vasculitis in adults. **Inclusion criteria** All adult patients suffering from an episode of AKF and/or proteinuria and hematuria with a kidney biopsy showing severe acute GN with crescents, glomerular necrosis or other histological evidence of vasculitis. AKF was as defined by the included studies. **Exclusion criteria** 1. RPGN with granular immune deposits such as SLE, cryoglobulinemia, HSP. 2. RPGN secondary to infections. 3. Polyarteritis nodosa. 4. Churg Strauss disease. 5. Goodpasture's disease	1. Corticosteroids versus placebo. 2. Non-corticosteroid agents, including Cyc, AZA, plasma exchange and immunoadsorption, with or without concurrent use of other immunosuppressive agents. 3. Different doses and duration of corticosteroid treatment. 4. Different doses, duration and route of administration of non-corticosteroid treatment 5. Any other agents evaluated in a RCT	1. Mortality at 1, 2 and 5 years. 2. Kidney function: SCr) level at 1, 2, 3, 6 and 12 months then annually. 3. Need for RRT at 1, 2, 3, 6 and 12 months then annually. 4. No. of patients relapsing (as defined by the study). 5. Adverse effects of each drug (e.g. nausea, leukopenia, and infections). 6. Cumulative doses of steroid and other agents. 7. Relapse of disease is defined by the included studies, but typically included an increase in BVAS score or a recurrence of symptoms of vasculitis.	1. On current data, the use of pulse Cyc results in an increased risk of relapse when compared to continuous use but a reduced total dose.	Is eligibility criteria similar to the guideline Are there any limitations to systematic review methodology Is limitation to evidence clearly addressed by the authors	Yes
Description of limitations of evidence by authors	The review is limited by the small number of available studies and some design features of the included studies. Several included diagnoses other than renal vasculitis. Some date prior to the development of the ANCA assay. This will limit the validity of the data and diagnoses included in those studies. Other differences include those between interventions, notably the regimens of immunosuppressive drugs and the number and volume of plasma exchanges utilized. Some of these may have had a very significant impact on the outcomes of studies and may explain the level of heterogeneity in some of our results					

Author, Year, RefID	Intervention	Control	Outcome	N studies (N intervention group/ total N)	Pooled OR[1](95% CI)	*P*-value	Test for heterogeneity	
							I^2 Statistic	*P*-value
Walters 2008[84] Study Yrs. :1980-2007	Pulse Cyc	Continuous Cyc	Death at 3 months	1(12/32)	1.67 [0.27, 10.33]	0.58	NA	NA
	Pulse Cyc	Continuous Cyc	Death at 6 months	1(12/32)	1.11 [0.22, 5.73]	0.90	NA	NA
	Pulse Cyc	Continuous Cyc	Death at 1 year	2(39/82)	0.82 [0.25, 2.72]	0.75	44	0.18
	Pulse Cyc	Continuous Cyc	Death at 2 years	3(61/129)	0.75 [0.21, 2.61]	0.65	56	0.11
	Pulse Cyc	Continuous Cyc	Death at 5 years	0	0	NA	NA	NA
	Pulse Cyc	Continuous Cyc	Death at final FU	3(61/129)	0.87 [0.42, 1.80]	0.71	32	0.23
	Pulse Cyc	Continuous Cyc	Dialysis at 1 month	0	0	NA	NA	NA
	Pulse Cyc	Continuous Cyc	Dialysis at 2 months	0	0	NA	NA	NA
	Pulse Cyc	Continuous Cyc	Dialysis at 3 months	0	0	NA	NA	NA
	Pulse Cyc	Continuous Cyc	Dialysis at 6 months	1(27/50)	6.00 [0.33, 110.43]	0.23	NA	NA
	Pulse Cyc	Continuous Cyc	Dialysis at 12months	0	0	NA	NA	NA
	Pulse Cyc	Continuous Cyc	Dialysis end of study	3(61/129)	1.70 [0.78, 3.67]	0.18	0	0.66
	Pulse Cyc	Continuous Cyc	Scr at 1 month	0	0	NA	NA	NA
	Pulse Cyc	Continuous Cyc	Scr at 2 months	0	0	NA	NA	NA
	Pulse Cyc	Continuous Cyc	Scr at 3 months	1(10/28)	-4.58 [-97.77, 88.61]	0.92	NA	NA
	Pulse Cyc	Continuous Cyc	Scr at 6 months	1(10/27)	51.69 [-81.03, 184.41]	0.45	NA	NA
	Pulse Cyc	Continuous Cyc	Scr at 12 months	2(21/52)	-9.78 [-53.16, 33.61]	0.66	0	0.98
	Pulse Cyc	Continuous Cyc	Scr at 2 years	2(21/52)	0	0.90	0	0.81

Author, Year, RefID	Intervention	Control	Outcome	N studies (N intervention group/ total N)	Pooled OR[1](95% CI)	*P*-value	Test for heterogeneity	
							I^2 Statistic	*P*-value
Walters 2008[84] Study Years :1980-2007	Pulse Cyc	Continuous Cyc	Remission at 6 months	1(27/50)	1.14 [0.88, 1.46]	0.32	NA	NA
	Pulse Cyc	Continuous Cyc	Untimed remission	1(22/47)	1.18 [0.98, 1.42]	0.077	NA	NA
	Pulse Cyc	Continuous Cyc	Total	2(49/97)	1.17 [1.00, 1.35]	0.044	0	0.79
	Pulse Cyc	Continuous Cyc	Relapse at 1 year	1(22/47)	2.84 [0.61, 13.21]	0.18	NA	NA
	Pulse Cyc	Continuous Cyc	Relapse at 2 years	1(22/47)	1.89 [0.51, 7.03]	0.34	NA	NA
	Pulse Cyc	Continuous Cyc	Untimed relapse	3(57/119)	1.75 [1.00, 3.05]	0.050	0	0.54
	Pulse Cyc	Continuous Cyc	Treatment failure	2(39/82)	1.36 [0.15, 12.56]	0.79	69	0.07
	Pulse Cyc	Continuous Cyc	Serious infections	3(61/129)	0.71 [0.32, 1.58]	0.40	80	0.01
	Pulse Cyc	Continuous Cyc	Leukopenia	3(61/129)	0.43 [0.22, 0.84]	0.014	0	0.54
	Pulse Cyc	Continuous Cyc	Nausea	2(49/97)	2.51 [1.07, 5.89]	0.035	0	0.99

Supplementary table 98. Summary table of RCT examining the effect of induction with pulse Cyc vs. daily p.o. Cyc in patients with ANCA vasculitis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
Mortality												
Death	de Groot 2009[18] EU/Mexico	6 mo (6 mo)	Pulse Cyc	Daily p.o. Cyc	76 (76)	73 (73)	S_{Cr} 225 µmol/l/ S_{Cr} 2.55 mg/dl GFR 38 ml/min/1.73 m^2	nd	5 (7%) [9 (2%)]	RR 0.53 (0.19-1.52) [257]	NS (0.79)	Fair
RRT/ Doubling of Scr												
ESRD	de Groot 2009[18] EU/Mexico	18 mo (6 mo)	Pulse Cyc	Daily p.o. Cyc	76 (76)	73 (73)	S_{Cr} 225 µmol/l/ S_{Cr} 2.55 mg/dl GFR 38 ml/min/1.73 m^2	nd	5 (7%) [1 (1%)]	RR 4.80 (0.57-40.13) [258]	NS (0.105)	Fair
Remission												
Remission	de Groot 2009[18] EU/Mexico	3 mo (6 mo)	Pulse Cyc	Daily p.o. Cyc	72 (76)	65 (73)	S_{Cr} 225 µmol/l/ S_{Cr} 2.55 mg/dl GFR 38 ml/min/1.73 m^2	nd	49 (68%) [43 (66%)]	RR 1.03 (0.81-1.30) [259]	nd	Fair
		6 mo (6 mo)			66 (76)	60 (73)			61 (92%) [55 (92%)]	RR 1.01 (0.91-1.12) [260]	nd	Fair
		9 mo (6 mo)			63 (76)	58 (73)			61 (97%) [58 (100%)]	RR 0.97 (0.93-1.01)[261]	nd	Fair
		12 mo (6 mo)			62 (76)	55 (73)			61 (98%) [55 (100%)]	RR 0.98 (0.95-1.02) [262]	nd	Fair
		15 mo (6 mo)			62 (76)	54 (73)			61 (98%) [54 (100%)]	RR 0.98 (0.95-1.02) [263]	nd	Fair
		18 mo (6 mo)			62 (76)	54 (73)			61 (98%) [54 (100%)]	RR 0.98 (0.95-1.02) [264]	nd	Fair
Relapse												

[257] Calculated by ERT
[258] Calculated by ERT
[259] Calculated by ERT
[260] Calculated by ERT
[261] Calculated by ERT
[262] Calculated by ERT
[263] Calculated by ERT
[264] Calculated by ERT

Relapse	de Groot 2009[1] EU/Mexico	>9 mo (6 mo)	Pulse Cyc	Daily p.o. Cyc	76 (76)	73 (73)	S_{Cr} 225 µmol/l/ S_{Cr} 2.55 mg/dl GFR 38 ml/min/1.73 m^2	nd	13 (17%) [6 (8%)	HR 2.01 (0.77- 5.30)	nd	Fair
Adverse events												
Any adverse event	de Groot 2009[18] EU/Mexico	9 mo (6 mo)	Pulse Cyc	Daily p.o. Cyc	76 (76)	73 (73)	S_{Cr} 225 µmol/l/ S_{Cr} 2.55 mg/dl GFR 38 ml/min/1.73 m^2	nd	58 (77%) [56 (77%)]	RR 0.99 (0.83-1.19) [265]	nd	Fair
Leukopenia									20 (26%) [33 (45%)]	RR 0.58 (0.37-0.92) [266]	0.016	Fair
Infection									20 (26%) [21 (29%)]	HR 0.41 (0.23-0.71)	nd	Fair
Serious/ life-threatening infection									7 (9%) [10 (14%)]	RR 0.67 (0.27-1.67) [267]	nd	Fair
Alopecia									0 (0%) [2 (3%)]	--	nd	Fair
Cancer									1 (1%) [1 (0%)]	--	nd	Fair
Hemorrhagic cystitis									2 (3%) [1 (1%)]	RR 1.92 (0.18-20.73) [268]	nd	Fair
Amenorrhea									1 (1%) [0 (0%)]	--	nd	Fair

[265] Calculated by ERT
[266] Calculated by ERT
[267] Calculated by ERT
[268] Calculated by ERT

Supplementary table 99. Summary table of RCT examining induction with pulse Cyc vs. daily p.o. Cyc in patients with ANCA vasculitis (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
S_{Cr}/GFR/CrCl													
Median eGFR improvement	de Groot 2009[18] EU/Mexico	9 mo (6 mo)	Pulse Cyc	Daily p.o. Cyc	76 (76)	73 (73)	S_{Cr} 225 µmol/l/ S_{Cr} 2.55 mg/dl GFR 38 ml/min/1.73 m^2	nd	ml/min/ 1.73 m^2	32 (29)	5 (8)	NS (0.36)	Fair

Supplementary table 100. Evidence profile of RCTS examining induction with rituximab vs. Cyc in patients with ANCA vasculitis

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	2 RCTs (High)	241 (132)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None	Moderate	No difference	Critical
ESRD	0 RCT	--	--	--	--	--	--	--	Critical
Remission	2 RCTs (High)	241 (132)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None	Moderate	No difference	High
Relapse	1 RCT (High)	44 (33)	No limitations (0)	N/A	Direct (0)	Sparse (-1)	Moderate	No difference	High
Proteinuria (categorical)	0 RCT	--	--	--	--	--	--	--	High
Kidney function (categorical)	0 RCT	--	--	--	--	--	--	--	High
ΔProteinuria (continuous)	0 RCT	--	--	--	--	--	--	--	Moderate
ΔKidney function (continuous)	2 RCTs (High)	241 (132)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None	Moderate	No difference	Moderate
Adverse events	2 RCTs (High)	241 (132)						No difference	Moderate

Balance of potential benefits and harm:
No difference

Quality of overall evidence:
Moderate

Supplementary table 101. Summary table of RCTs examining induction with rituximab vs. Cyc in patients with ANCA vasculitis (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results		*P* value	Quality
			Intervention	Control	Intervention	Control			Events (%) Intervention [Control]	RR/OR/HR		
Mortality												
Death	Jones 2010[43] EU & Australia	12 mo (6 mo for rituximab; 12 mo for Cyc)	Rituximab + i.v. Cyc	i.v. Cyc followed by AZA	33 (33)	11 (11)	GFR 20 ml/min/1.73 m^2	nd	6 (18%) [2 (18%)]	RR 1.00[269] (0.24-4.25)	NS (1.00)	Good
Death	Stone 2010[75] Multi	6 mo (6 mo)	i.v. rituximab + placebo Cyc	Cyc + placebo-rituximab	99 (99)	98 (98)	eCrCl 54 ml/min	nd	1 (1%) [2 (2%)]	RR 0.49 (0.05-5.37)	nd	Fair
Remission												
Sustained remission	Jones 2010[43] EU & Australia	12 mo (6 mo for rituximab; 12 mo for Cyc)	Rituximab + i.v. Cyc	i.v. Cyc followed by AZA	33 (33)	11 (11)	GFR 20 ml/min/1.73 m^2	nd	25 (76%) [9 (82%)]	RR 0.93[270] (0.66-1.30)	NS (0.68)	Good
Remission	Stone 2010[75] Multi	6 mo (6 mo)	i.v. rituximab + placebo Cyc	Cyc + placebo-rituximab	99 (99)	98 (98)	eCrCl 54 ml/min	nd	70 (71%) [61 (62%)]	RR 1.14 (0.93-1.39)	NS (0.10)	Fair
ANCA negative									47% [24%]	--	0.004	Fair
Proteinase 3-ANCA negative									15% [17%]	--	<0.001	Fair
Myeloperoxidase-ANCA negative									40% [41%]	--	NS (0.95)	Fair
Relapse												
Relapse	Jones 2010[43] EU & Australia	12 mo (6 mo for rituximab; 12 mo for Cyc)	Rituximab + i.v. Cyc	i.v. Cyc followed by AZA	33 (33)	11 (11)	GFR 20 ml/min/1.73 m^2	nd	4 (27%) [1 (10%)]	RR 1.33[271] (0.17-10.70)	NS (0.70)	Good
Adverse events												
Leukopenia	Jones 2010[43] EU & Australia	12 mo (6 mo for rituximab; 12 mo for Cyc)	Rituximab + i.v. Cyc	i.v. Cyc followed by AZA	33 (33)	11 (11)	GFR 20 ml/min/1.73 m^2	nd	2 (6%) [1 (9%)]	RR 0.67[272] (0.07-6.66)	nd	Good
All infections									12 (36%) [3 (27%)]	RR 1.44[273] (0.50-4.14)	nd	

[269] Calculated by ERT
[270] Calculated by ERT
[271] Calculated by ERT
[272] Calculated by ERT
[273] Calculated by ERT

Serious infection									6 (18%) [2 (18%)]	RR 1.00[274] (0.24-4.25)	nd	
All infusion reactions									2 (6%) [0 (0%)]	--	nd	
Cancer									2(6%) [0 (0%)]	--	nd	
Events requiring hospitalization or life-threatening									12 (36%) [4 (36%)]	RR 1.00[275] (0.41-2.47)	nd	
Cancer									1 (1%) [1 (1%)]	RR 0.99[276] (0.06-15.61)	nd	Fair
Leukopenia									3 (3%) [10 (10%)]	RR 0.30[277] (0.08-1.05)	nd	Fair
Thrombocytopenia									3 (3%) [1 (1%)]	RR 2.97[278] (0.31-28.06)	nd	Fair
Infection									7 (7%) [7 (7%)]	RR 0.99[279] (0.36-2.72)	nd	Fair
Hemorrhagic cystitis									1 (1%) [1 (1%)]	RR 0.99[280] (0.06-15.61)	nd	Fair
Hospitalization due to disease or treatment	Stone 2010[75] Multi	6 mo (6 mo)	i.v. rituximab + placebo Cyc	Cyc + placebo-rituximab	99 (99)	98 (98)	eCrCl 54 ml/min	nd	8 (8%) [2 (2%)]	RR 3.96[281] (0.86-18.18)	nd	Fair
Infusion reaction preventing further infusions of investigational medication									1 (1%) [0 (0%)]	--	nd	Fair
All AEs									1035 [1016]	--	nd	Fair
All serious AEs									79 [78]	--	nd	Fair

[274] Calculated by ERT
[275] Calculated by ERT
[276] Calculated by ERT
[277] Calculated by ERT
[278] Calculated by ERT
[279] Calculated by ERT
[280] Calculated by ERT
[281] Calculated by ERT

Supplementary table 102. Summary table of RCTs examining induction with rituxamib vs. Cyc in patients with ANCA vasculitis (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	Results			*P* value	Quality
			Intervention	Control	Intervention	Control			Units	Baseline Intervention (Control)	Δ Intervention (Control)		
S_{Cr}/GFR/CrCl													
Median ↑eGFR	Jones 2010[43] EU & Australia	12 mo (6 mo for rituxamib; 12 mo for Cyc)	Rituximab + i.v. Cyc	i.v. Cyc followed by AZA	33 (33)	11 (11)	GFR 20 ml/min/ 1.73 m^2	nd	ml/min/1 .73 m^2	20 (12)	29 (27)	NS (0.14)	Good
ΔeCrCl	Stone 2010[75] Multi	6 mo (6 mo)	i.v. rituximab + placebo Cyc	Cyc + placebo-rituximab	99 (99)	98 (98)	eCrCl 54 ml/min	nd	ml/min	54 (69)	+11.2 (+10.5)	nd	Fair

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