NEPHROLOGY

Nephrology 18 (2013) 71–72



COCHRANE COMMENTARIES

Edited by Angela Webster (angela.webster@sydney.edu.au) Written by Philip Masson (philip.masson@health.nsw.gov.au)

Induction and maintenance treatment of proliferative lupus nephritis

What is this review about?

The use of immunosuppressive treatment regimens for the induction and maintenance therapy of proliferative lupus nephritis (classes III, IV, V + III, V + IV).

What are the findings?

For treatment induction, in the short term (up to six months) treatment with mycophenolate mofetil (MMF) conferred similar risk of death and progression to end-stage kidney disease (ESKD) as conventional therapy with intravenous (IV) cyclophosphamide. Renal remission and renal relapse were equally likely with each agent. However, MMF was associated with a significantly reduced risk of ovarian failure, leucopenia and alopecia, but increased risk of diarrhoea. Optimal duration of MMF remains unclear and longer term outcome data were sparse. For maintenance treatment, MMF was associated with a significantly lower risk of renal relapse when compared with azathioprine.

What are the findings based on?

A total of 50 trials involving 2846 randomized participants. Seven trials (N = 710) compared MMF with IV cyclophosphamide for induction treatment. Three trials (N = 371)compared MMF with azathioprine for maintenance therapy. Disease spectrum and proportion of patients with each class of lupus nephritis differed among trials as did co-interventions, definitions of outcomes, length of follow up, and patient socioeconomic and environmental characteristics. Of nine trials (one trial compared both induction and maintenance therapy) contributing to the main conclusions, methodological quality was variable with inconsistent reporting of trial methodology. Allocation concealment was adequate in four trials and six studies reported adequate random sequence generation. No study described adequate blinding of objective and subjective outcomes. Incomplete outcome data was addressed in seven studies, the same number being free of selective reporting. Seven trials were analyzed by intention-to-treat analysis. The remaining 41 trials compared multiple diverse interventions such that informative meta-analysis was not possible.

Implications for practice

• MMF may be used in both induction and maintenance treatment of proliferative lupus nephritis

• For induction therapy MMF is as effective as IV cyclophosphamide at inducing complete remission in proteinuria and achieving stable renal function at six months with no difference in mortality or incidence of ESKD.

• MMF reduces the risk of ovarian failure, leucopenia and alopecia compared with IV cyclophosphamide, but is associated with an increased risk of diarrhoea.

• In maintenance therapy, MMF is superior to azathioprine for prevention of renal relapse but with no difference in incidence of ESKD or doubling of serum creatinine. Leucopenia is less common with MMF, but other adverse events are equally likely with either treatment.

Clinical perspective

This systematic review supports the use of MMF as first line therapy for induction immunosuppression for the treatment of proliferative lupus nephritis (Figure 1). Already established as an alternative to azathioprine in maintenance therapy, this meta-analysis confirms MMF has equivalent efficacy in achieving primary disease control, and preventing death and ESKD. Its favourable side-effect profile - particularly the lower observed incidence of ovarian failure - means that MMF should be considered as an option in primary therapy for women of reproductive age. MMF is more effective at preventing relapse and associated with fewer side-effects than azathioprine and should be considered first-line maintenance treatment. Newer biologic agents such as Rituximab - increasingly used in clinical practice - have only been evaluated in two small studies with inconsistent outcome reporting, thereby precluding their inclusion in data synthesis. Accordingly, their role in clinical management remains uncertain. Future research of immunosuppressive regimens requires larger strategic and pragmatic collaborative trials, with clinically relevant,

Study or Subgroup			IV Cyclophosph		Mainht	Risk Ratio	Veer	Risk Ratio
Mortality	Events	Total	Events	Total	weight	M-H, Random, 95% Cl	rear	M-H, Random, 95% Cl
-		74		~~	22.50		0005	
Ginzler 2005	4	71 19	8 1	69	33.5%	0.49 [0.15, 1.54]		
Ong 2005 Mulia Basia, 2000	1	19	1	25 25	6.1%	1.32 [0.09, 19.71]	2005 2008	
Mulic-Bacic 2008	1	20 10	0		4.5%	3.71 [0.16, 86.55]		
Sundel 2008			U 5	14	4.6%	4.09 [0.18, 91.23]		
Appel 2009	9 1	185		185	38.6%	1.80 [0.61, 5.27]	2009	
Li 2009f		20	2	20	8.3%	0.50 (0.05, 5.08)		
El-Shafey 2010 Subtotal (95% Cl)	0	24 349	1	23	4.5% 100.0%	0.32 [0.01, 7.48] 1.02 [0.52, 1.98]	2010	
Total events	17	345	17	501	100.070	102 [0.52, 1.50]		
Heterogeneity: Tau ² =		Z - 6.00		V IZ - 0.06				
Test for overall effect:), 1 – 0 %				
restion overall ellect.	. Z = 0.00 (,г — 0.90	<i>"</i>					
Complete rena	al remissi	on						
Ginzler 2005	16	71	4	69	9.6%	3.89 [1.37, 11.05]	2005	
Ong 2005	5	19	3	25	6.4%	2.19 [0.60, 8.06]	2005	
Mulic-Bacic 2008	14	20	15	25	39.2%	1.17 [0.76, 1.79]	2008	
Li 2009f	9	20	6	20	14.6%	1.50 [0.66, 3.43]	2009	
Appel 2009	16	185	15	185	20.5%	1.07 [0.54, 2.09]	2009	_ _
El-Shafey 2010	6	24	5	23	9.7%	1.15 [0.41, 3.25]	2010	
Subtotal (95% CI)		339		347	100.0%	1.39 [0.99, 1.95]		◆
Total events	66		48					
Heterogeneity: Tau ^z =	= 0.03; Chi		df= 5 (P = 0.32); I ≈ = 159	Хо			
	= 0.03; Chi		df= 5 (P = 0.32); I ≭ = 159	%			
Heterogeneity: Tau ^z =	= 0.03; Chi : Z = 1.89 (df= 5 (P = 0.32); I ² = 159	%			
Heterogeneity: Tau ^z = Test for overall effect:	= 0.03; Chi : Z = 1.89 (df= 5 (P = 0.32); I² = 159 69	% 32.0%	0.21 (0.01, 4.34)	2005	
Heterogeneity: Tau ^z = Test for overall effect: Ovarian Failu r	= 0.03; Chi : Z = 1.89 (e	(P = 0.06 65 184	, df= 5 (P = 0.32 3)	69 180	32.0% 68.0%	0.21 (0.01, 4.34) 0.12 (0.02, 0.97)	2005 2009	
Heterogeneity: Tau ² = Test for overall effect: Ovarian Failur Ginzler 2005	= 0.03; Chi : Z = 1.89 (e 0	(P = 0.06 65	, df = 5 (P = 0.32 3) 2	69 180	32.0%			
Heterogeneity: Tau ² = Test for overall effect Ovarian Failur Ginzler 2005 Appel 2009	= 0.03; Chi : Z = 1.89 (e 0	(P = 0.06 65 184	, df = 5 (P = 0.32 3) 2	69 180	32.0% 68.0%	0.12 [0.02, 0.97]		
Heterogeneity: Tau ² = Test for overall effect: Ovarian Failur Ginzler 2005 Appel 2009 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	= 0.03; Chi : Z = 1.89 (e 0 1 = 0.00; Chi	P = 0.08 65 184 249 ² = 0.09	, df= 5 (P = 0.32 3) 2 8 , df= 1 (P = 0.77	69 180 249	32.0% 68.0% 100.0 %	0.12 [0.02, 0.97]		
Heterogeneity: Tau ² = Test for overall effect: Ovarian Failur Ginzler 2005 Appel 2009 Subtotal (95% CI) Total events	= 0.03; Chi : Z = 1.89 (e 0 1 = 0.00; Chi	P = 0.08 65 184 249 ² = 0.09	, df= 5 (P = 0.32 3) 2 8 , df= 1 (P = 0.77	69 180 249	32.0% 68.0% 100.0 %	0.12 [0.02, 0.97]		
Heterogeneity: Tau ² = Test for overall effect: Ovarian Failur Ginzler 2005 Appel 2009 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	= 0.03; Chi : Z = 1.89 (e 0 1 = 0.00; Chi	P = 0.08 65 184 249 ² = 0.09	, df= 5 (P = 0.32 3) 2 8 , df= 1 (P = 0.77	69 180 249	32.0% 68.0% 100.0 %	0.12 [0.02, 0.97]		
Heterogeneity: Tau ^a = Test for overall effect: Ovarian Failur Ginzler 2005 Appel 2009 Subtotal (95% CI) Total events Heterogeneity: Tau ^a = Test for overall effect:	= 0.03; Chi : Z = 1.89 (e 0 1 = 0.00; Chi	P = 0.08 65 184 249 ² = 0.09	, df= 5 (P = 0.32 3) 2 8 , df= 1 (P = 0.77	69 180 249	32.0% 68.0% 100.0 %	0.12 [0.02, 0.97]	2009	
Heterogeneity: Tau ^a = Test for overall effect: Ovarian Failur Ginzler 2005 Appel 2009 Subtotal (95% CI) Total events Heterogeneity: Tau ^a = Test for overall effect: Leucopenia	= 0.03; Chi : Z = 1.89 (e 0 1 = 0.00; Chi : Z = 2.21 ((P = 0.0) 65 184 249 7 = 0.09 (P = 0.0)	, df= 5 (P = 0.32 3) 2 8 , df= 1 (P = 0.77 3)	69 180 249); I ² = 0%	32.0% 68.0% 100.0 %	0.12 (0.02, 0.97) 0.15 (0.03, 0.80)	2009 2005	
Heterogeneity: Tau ² = Test for overall effect: Ovarian Failur Ginzler 2005 Appel 2009 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Leucopenia Ong 2005	= 0.03; Chi : Z = 1.89 (e 0 1 = 0.00; Chi : Z = 2.21 (7	(P = 0.06 65 184 249 (P = 0.09 (P = 0.03 19	, df= 5 (P = 0.32 3) 2 8 , df= 1 (P = 0.77 3) 13	69 180 249); ²= 0% 25	32.0% 68.0% 100.0 % 29.6%	0.12 (0.02, 0.97) 0.15 (0.03, 0.80) 0.71 (0.35, 1.43)	2009 2005 2005	
Heterogeneity: Tau ² = Test for overall effect: Ovarian Failur Ginzler 2005 Appel 2009 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Leucopenia Ong 2005 Ginzler 2005	: 0.03; Chi Z = 1.89 (e 0 1 ≠ 0.00; Chi Z = 2.21 (7 5	(P = 0.06 65 184 249 (P = 0.09 (P = 0.03 19 83	, df= 5 (P = 0.32 3) 2 8 , df= 1 (P = 0.77 3) 13 14	69 180 249); ² = 0% 25 75	32.0% 68.0% 100.0 % 29.6% 21.1% 4.2%	0.12 (0.02, 0.97) 0.15 (0.03, 0.80) 0.71 (0.35, 1.43) 0.32 (0.12, 0.85)	2009 2005 2005 2009	
Heterogeneity: Tau ² = Test for overall effect: Ovarian Failur Ginzler 2005 Appel 2009 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Leucopenia Ong 2005 Ginzler 2005 Li 2009f	: 0.03; Chi Z = 1.89 (e 0 1 : 0.00; Chi Z = 2.21 (7 5 1	(P = 0.06 65 184 249 (P = 0.09 (P = 0.03 19 83 20	, df= 5 (P = 0.32 3) 2 8 , df= 1 (P = 0.77 3) 13 14 1	69 180 249); ² = 0% 25 75 20	32.0% 68.0% 100.0 % 29.6% 21.1% 4.2% 31.9%	0.12 (0.02, 0.97) 0.15 (0.03, 0.80) 0.71 (0.35, 1.43) 0.32 (0.12, 0.85) 1.00 (0.07, 14.90)	2009 2005 2005 2009 2009	
Heterogeneity: Tau ² = Test for overall effect: Ovarian Failur Ginzler 2005 Appel 2009 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Leucopenia Ong 2005 Ginzler 2005 Li 2009f Appel 2009	= 0.03; Chi Z = 1.89 (e 0 1 = 0.00; Chi Z = 2.21 (7 5 1 11	(P = 0.06 65 184 249 (P = 0.09 (P = 0.03 19 83 20 184	, df= 5 (P = 0.32)) 2 8 10 , df= 1 (P = 0.77)) 13 14 1 38	69 180 249); ² = 0% 25 75 20 180 23	32.0% 68.0% 100.0 % 29.6% 21.1% 4.2% 31.9%	0.12 (0.02, 0.97) 0.15 (0.03, 0.80) 0.71 (0.35, 1.43) 0.32 (0.12, 0.85) 1.00 (0.07, 14.90) 0.28 (0.15, 0.54)	2009 2005 2005 2009 2009	
Heterogeneity: Tau ^a = Test for overall effect: Ovarian Failur Ginzler 2005 Appel 2009 Subtotal (95% CI) Total events Heterogeneity: Tau ^a = Test for overall effect: Leucopenia Ong 2005 Ginzler 2005 Ginzler 2005 Li 2009f Appel 2009 El-Shafey 2010	= 0.03; Chi Z = 1.89 (e 0 1 = 0.00; Chi Z = 2.21 (7 5 1 11	(P = 0.06 65 184 249 (P = 0.09 (P = 0.03 (P = 0.03 19 83 20 184 24	, df= 5 (P = 0.32)) 2 8 10 , df= 1 (P = 0.77)) 13 14 1 38	69 180 249); ² = 0% 25 75 20 180 23	32.0% 68.0% 100.0 % 29.6% 21.1% 4.2% 31.9% 13.1%	0.12 (0.02, 0.97) 0.15 (0.03, 0.80) 0.32 (0.12, 0.85) 1.00 (0.07, 14.80) 0.28 (0.15, 0.54) 1.28 (0.32, 5.10)	2009 2005 2005 2009 2009	
Heterogeneity: Tau ^a = Test for overall effect: Ovarian Failur Ginzler 2005 Appel 2009 Subtotal (95% CI) Total events Heterogeneity: Tau ^a = Test for overall effect: Leucopenia Ong 2005 Ginzler 2005 Ginzler 2005 Li 2009f Appel 2009 EI-Shafey 2010 Subtotal (95% CI)	: 0.03; Chi Z = 1.89 (e 0 1 : 0.00; Chi Z = 2.21 (7 5 1 11 4 28	(P = 0.00 65 184 249 (P = 0.09 (P = 0.03 (P = 0.03 19 83 20 184 24 330	, df= 5 (P = 0.32)) 2 8 10 , df= 1 (P = 0.77)) 13 14 1 38 3 69	69 180 249); ² = 0% 25 75 20 180 23 323	32.0% 88.0% 100. 0% 21.1% 4.2% 31.9% 13.1% 100.0 %	0.12 (0.02, 0.97) 0.15 (0.03, 0.80) 0.32 (0.12, 0.85) 1.00 (0.07, 14.80) 0.28 (0.15, 0.54) 1.28 (0.32, 5.10)	2009 2005 2005 2009 2009	
Heterogeneity: Tau ^a = Test for overall effect: Ovarian Failur Ginzler 2005 Appel 2009 Subtotal (95% CI) Total events Heterogeneity: Tau ^a = Test for overall effect: Leucopenia Ong 2005 Ginzler 2005 Li 2009f Appel 2009 EI-Shafey 2010 Subtotal (95% CI) Total events	: 0.03; Chi Z = 1.89 (e 0 1 : 0.00; Chi Z = 2.21 (7 5 1 1 4 28 : 0.17; Chi	(P = 0.00 65 184 249 (P = 0.03 (P = 0.03 19 83 20 184 24 330 P = 6.81	, df= 5 (P = 0.32) 2 8 10 10 , df= 1 (P = 0.77) 13 14 1 38 3 , df= 4 (P = 0.15	69 180 249); ² = 0% 25 75 20 180 23 323	32.0% 88.0% 100.0% 29.6% 21.1% 4.2% 31.9% 13.1% 13.1%	0.12 (0.02, 0.97) 0.15 (0.03, 0.80) 0.32 (0.12, 0.85) 1.00 (0.07, 14.80) 0.28 (0.15, 0.54) 1.28 (0.32, 5.10)	2009 2005 2005 2009 2009	
Heterogeneity: Tau ^a = Test for overall effect: Ovarian Failur Ginzler 2005 Appel 2009 Subtotal (95% CI) Total events Heterogeneity: Tau ^a = Test for overall effect: Leucopenia Ong 2005 Ginzler 2005 Li 2009f Appel 2009 EI-Shafey 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ^a =	: 0.03; Chi Z = 1.89 (e 0 1 : 0.00; Chi Z = 2.21 (7 5 1 1 4 28 : 0.17; Chi	(P = 0.00 65 184 249 (P = 0.03 (P = 0.03 19 83 20 184 24 330 P = 6.81	, df= 5 (P = 0.32) 2 8 10 10 , df= 1 (P = 0.77) 13 14 1 38 3 , df= 4 (P = 0.15	69 180 249); ² = 0% 25 75 20 180 23 323	32.0% 88.0% 100.0% 29.6% 21.1% 4.2% 31.9% 13.1% 13.1%	0.12 (0.02, 0.97) 0.15 (0.03, 0.80) 0.32 (0.12, 0.85) 1.00 (0.07, 14.80) 0.28 (0.15, 0.54) 1.28 (0.32, 5.10)	2009 2005 2005 2009 2009	
Heterogeneity: Tau ^a = Test for overall effect: Ovarian Failur Ginzler 2005 Appel 2009 Subtotal (95% CI) Total events Heterogeneity: Tau ^a = Test for overall effect: Leucopenia Ong 2005 Ginzler 2005 Li 2009f Appel 2009 EI-Shafey 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ^a =	: 0.03; Chi Z = 1.89 (e 0 1 : 0.00; Chi Z = 2.21 (7 5 1 1 4 28 : 0.17; Chi	(P = 0.00 65 184 249 (P = 0.03 (P = 0.03 19 83 20 184 24 330 P = 6.81	, df= 5 (P = 0.32) 2 8 10 10 , df= 1 (P = 0.77) 13 14 1 38 3 , df= 4 (P = 0.15	69 180 249); ² = 0% 25 75 20 180 23 323	32.0% 88.0% 100.0% 29.6% 21.1% 4.2% 31.9% 13.1% 13.1%	0.12 (0.02, 0.97) 0.15 (0.03, 0.80) 0.32 (0.12, 0.85) 1.00 (0.07, 14.80) 0.28 (0.15, 0.54) 1.28 (0.32, 5.10)	2009 2005 2005 2009 2009	

Fig. 1 MMF versus IV Cyclophosphamide as induction therapy for lupus nephritis: Main outcomes and adverse events.

long-term follow-up outcomes to fully clarify risks and eventual harms of treatments, optimal treatment duration and route of administration.

Citation of Cochrane Review and 'assessed as up to date' or published date – please confirm with Narelle Willis NarellW2@chw.edu.au

Henderson LK, Masson P, Craig JC, Roberts MA, Flanc RS, Strippoli GFM, **Webster AC**. Induction and maintenance treatment of proliferative lupus nephritis: a meta-analysis of randomized controlled trials. *Cochrane Database of Systematic Reviews* 2012, *[in press]*.