NEPHROLOGY

Nephrology **18** (2013) 71–72 doi:10.1111/nep.12011

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,

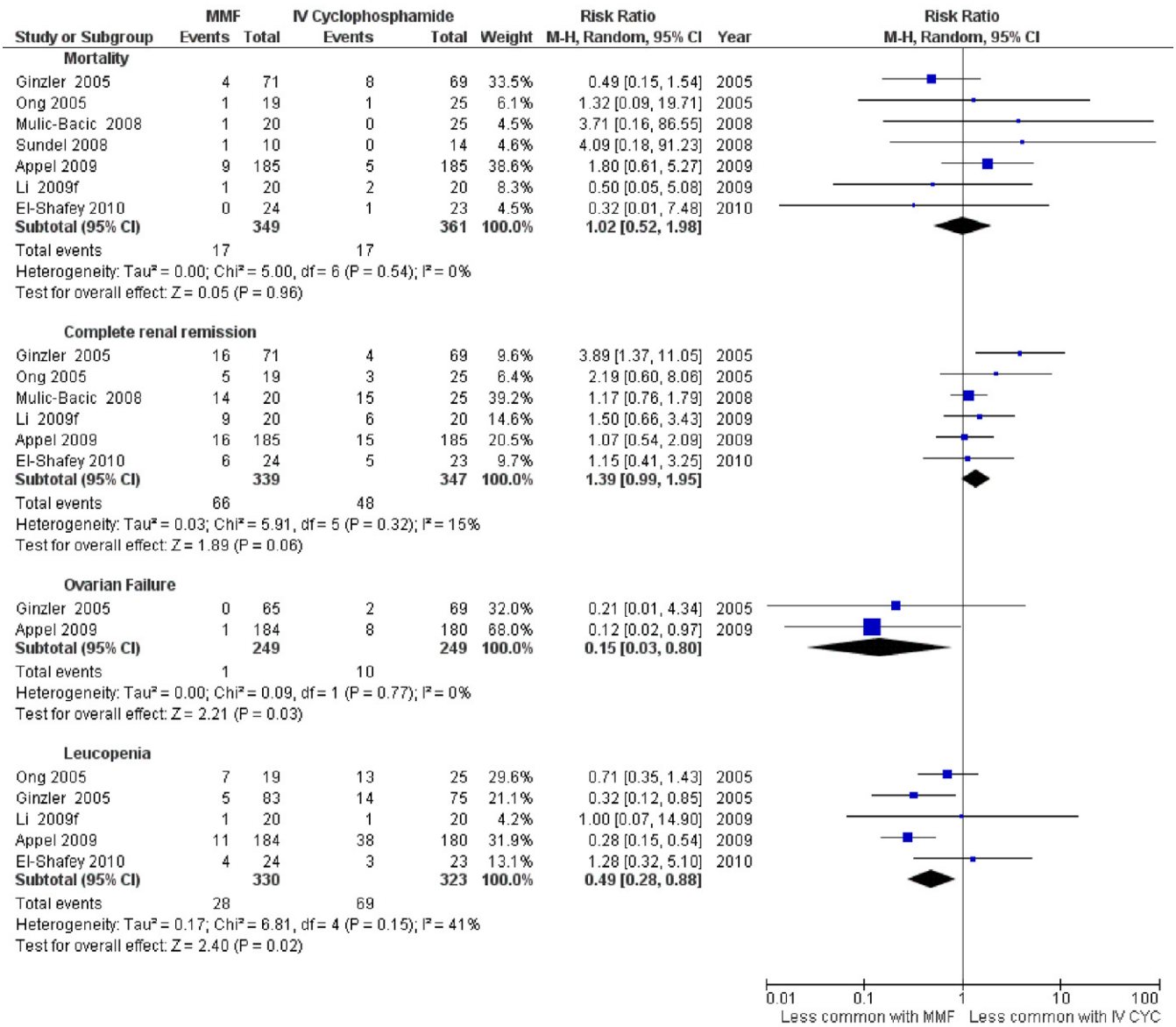

Fig. 1 MMF versus IV Cyclophosphamide as induction therapy for lupus nephritis: Main outcomes and adverse events.

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]*.