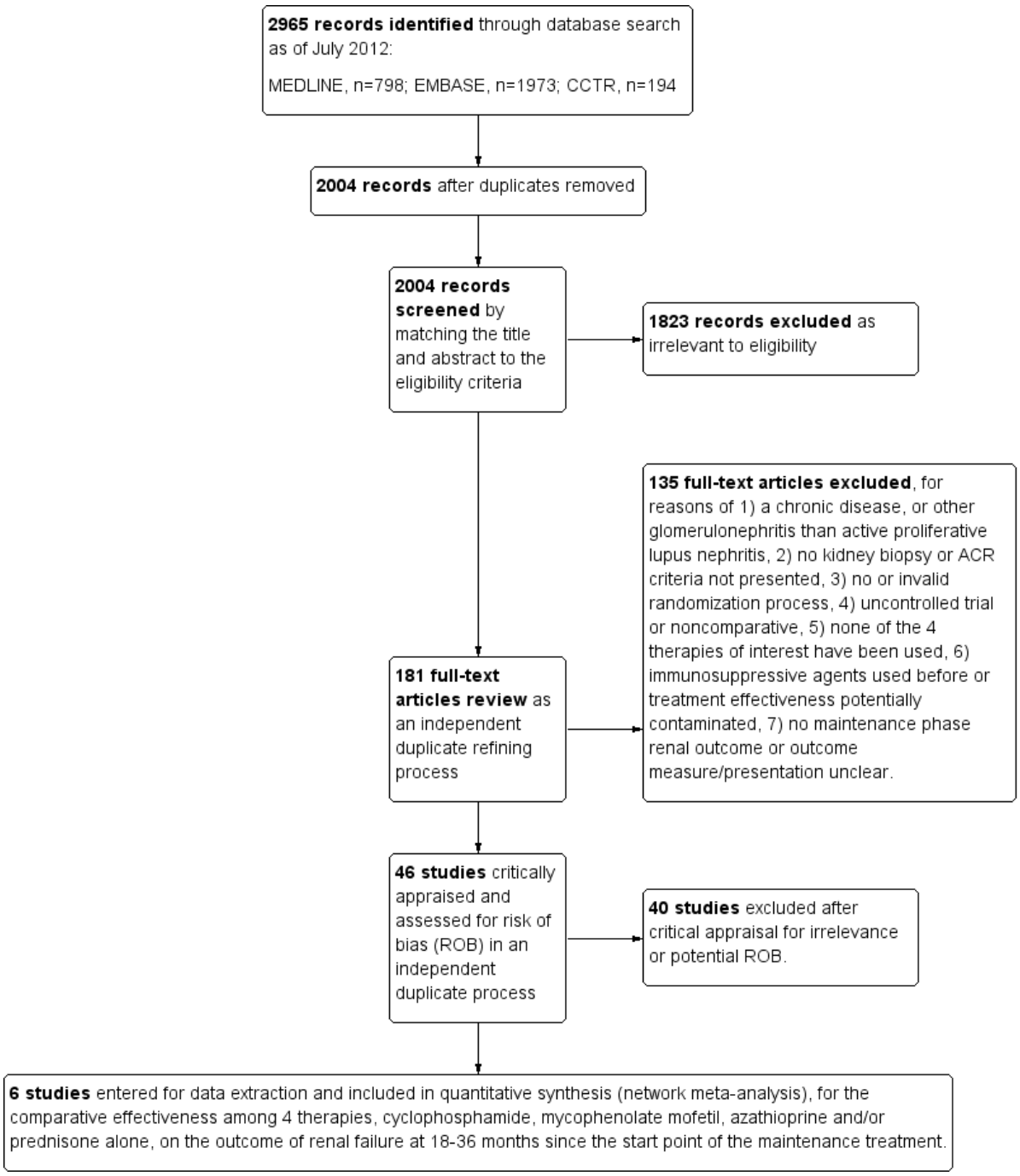
Online supplement to: Immunosuppressive Therapies for the Maintenance Treatment of Proliferative Lupus Nephritis: A Systematic Review and Network Metaanalysis. *The Journal of Rheumatology.* doi:10.3899/jrheum.141650

Appendix A. Flowchart of Study Selection

Figure A presents the flowchart of the literature search and study selection process.



Appendix B. Model Specification

Model parametrization follows the standards of the Bayesian Inference using Gibbs Sampler (BUGS) code for combining 3-arm trials, as recommended in the Introductory Document on the website of the Mixed Treatment Comparisons, University of Bristol [27] - URL: http://www.bris.ac.uk/social-community-medicine/projects/mpes/mtc/; and on the website of the International Society for Pharmacoeconomics and Outcomes Research [28]. - URL: http://www.ispor.org/publications/value/ViHsupplementary/ViH13i8_Ades.asp

B.1 Likelihood

This is a stochastic process drawing the parameter p_{st} from a binomial likelihood distribution:

$$r_{st} \sim \text{Binom}(n_{st}, p_{st})$$

which is based on a logistic model of the deterministic relationship between treatment effects and the parameter p_{st} , as given by:

$$\text{logit}(p_{st}) = \begin{cases} \mu_{sb} & t = b \\ \mu_{sb} + \delta_{stb} & t \neq b \end{cases}$$

where r_{st} is the number of responses in the treatment arm t of study s; n_{st} is the sample size of the treatment arm t of study s; and p_{st} is the expected probability of response for the treatment arm t of study s; μ_{sb} is the log odds of the baseline treatment b's effect in study s (and baseline treatment is allowed to vary between studies); and δ_{stb} is the log odds ratio of a treatment t's effect relative to the baseline treatment b in any given study, where t is different from b.

B.2 The Nodes

The study effects μ_{sb} are handled as uncorrelated nuisance parameters (nodes) - not of estimation interest, but important for the estimation of the other nodes - which represent the baseline treatment effects in the studies, and is often the standard of care in a study that has all other treatments compared to. These nodes are measured in the log odds scale.

The other treatment effects as captured in δ_{stb}, when t is not b, are the basic nodes, which represent the relative effects between any two treatments that are directly compared to baseline treatments in the studies. Indirect comparisons are made possible by contrasting between basic nodes between studies, which are called functional nodes that are computed using basic nodes. These relative effects are measured in the log odds ratio scale.

B.3 Random Effects

Between-study heterogeneity is measured using the study-specific random effects between the nodes δ_{stb} (random intercepts, and random slopes that capture the study x treatment interaction). There are two components of variation in these nodes. One component is resulting from the underlying true difference in the effect between any pairwise comparison of the treatments (the systematic component); an additional component is the random variation between studies and treatments resulted from heterogeneity. The random component is measured using random effects existing between these nodes, expressed by a homogeneous variance node σ^2 that is pooled over studies, accounting for the magnitude of heterogeneity. As shown in the following stochastic process, the study-specific node, log odds ratios δ_{stb} of treatment effects relative to baseline, is drawn from a normal likelihood distribution with two components:

$$\delta_{stb} \sim \mathrm{Norm}(d_t - d_b, \sigma^2)$$

where the stochastic nodes d_t and d_b are of main expectation interest, which are the underlying true treatment effects pooled over studies that are measured in the log odds scale, and d_t–d_b are the true differences between any two treatments that are measured in the log odds ratio scale. These are the signal (or systematic) component. The variance part σ^2 measures random variation between studie-treatments, accounting for the random effects of δ_{stb}, which is the noise (or random) component.

The common node σ is drawn from a vague (flat) prior distribution:

$$\sigma \sim \mathrm{Unif}(0, 2)$$

This is done for the synthesis of 2-arm trials.

B.4 Three-arm Trials

When there are 3 arms in a trial, a covariance term is introduced between the two log odds ratios δ_{stb}, where t=(1,2) when both compared to baseline treatment b (and s, b are fixed in a specific study). Under the assumption of homogeneous variation between studies, expressed by the common node σ as shown above, it is suggested that the covariance is [42, 43]:

$$\mathrm{Cov}(\delta_{st1b}, \delta_{st2b}) = \frac{\sigma^2}{2}$$

The multivariate normal (MVN) distribution is given by: $\tilde{\delta} \sim \mathrm{MVN}(\tilde{\mu}, \Sigma)$, where $\tilde{\delta}$ is a vector of Gaussian random variables - the sampling distribution of log odds ratios is asymptotically normal according to the Central Limit Theorem. The joint distribution of two vectors of Gaussian random variables $\tilde{\delta}_{stb}, t = (1,2)$ (and s, b are fixed), is then given by:

$$\begin{pmatrix} \tilde{\delta}_1 \\ \\ \tilde{\delta}_2 \end{pmatrix} \sim \mathrm{MVN}\left(\begin{pmatrix} \tilde{\mu}_1 \\ \\ \tilde{\mu}_2 \end{pmatrix}, \begin{pmatrix} \Sigma_{11} & \Sigma_{12} \\ \\ \Sigma'_{12} & \Sigma_{22} \end{pmatrix} \right)$$

$$\tilde{\delta}_1 | (\tilde{\delta}_2 = \delta_2) \sim \mathrm{MVN}(\tilde{\mu}_1 + \Sigma_{12}\Sigma_{22}^{-1}(\delta_2 - \tilde{\mu}_2),\ \Sigma_{11} - \Sigma_{12}\Sigma_{22}^{-1}\Sigma'_{12})$$

where $\tilde{\mu}_1 = \tilde{b}_1 - \tilde{b}_b$, $\tilde{\mu}_2 = \tilde{b}_2 - \tilde{b}_b$, the true unknowns pooled over studies; and $\Sigma_{21} = \Sigma'_{12}$.

Then we have the joint distribution for the scalar form of two random variables $\tilde{\delta}_1 = \delta_1$ and $\tilde{\delta}_2 = \delta_2$:

$$\begin{pmatrix} \delta_1 \\ \\ \delta_2 \end{pmatrix} \sim \mathrm{MVN}\left(\begin{pmatrix} \mu_1 \\ \\ \mu_2 \end{pmatrix}, \begin{pmatrix} \sigma^2 & \frac{\sigma^2}{2} \\ \\ \frac{\sigma^2}{2} & \sigma^2 \end{pmatrix} \right)$$

and the decomposition of the above equation for the univariate marginal (unconditional) distribution of δ_1, the univariate conditional distribution of $\delta_2|\delta_1$, respectively, is given by:

$$\begin{aligned} \delta_1 &\sim \mathrm{N}(\mu_1,\ \sigma^2) \\ \delta_2|\delta_1 &\sim \mathrm{N}(\mu_2 + \Sigma'_{12}\Sigma_{11}^{-1}(\delta_1 - \mu_1),\ \Sigma_{22} - \Sigma'_{12}\Sigma_{11}^{-1}\Sigma_{12}) \\ &= \mathrm{N}(\mu_2 + \frac{\sigma^2}{2}\frac{1}{\sigma^2}(\delta_1 - \mu_1),\ \sigma^2 - \frac{\sigma^2}{2}\frac{1}{\sigma^2}\frac{\sigma^2}{2}) \\ &= \mathrm{N}(\mu_2 + \frac{1}{2}(\delta_1 - \mu_1),\ \frac{3}{4}\sigma^2) \end{aligned}$$

where $\mu_1 = d_1 - d_b$, $\mu_2 = d_2 - d_b$, the true unknowns for a specific study; and σ^2 is assumed to be a fixed constant pooled over studies that measures the randomness as discussed above.

In a specific 3-arm trial 's', relative to the baseline treatment b, the log odds ratios of the other 2 arms δ_{stb} , $t = (1,2)$ are therefore drawn using the following stochastic process - one at a time with the second node conditional on the first one:

$$\delta_1 \sim \mathrm{N}(\mu_1, \sigma^2)$$

$$\delta_2|\delta_1 \sim \mathrm{N}(\mu_2', \frac{3}{4}\sigma^2)$$

where $\mu_1 = d_1 - d_b$, and $\mu_2' = \mu_2 + \frac{1}{2}(\delta_1 - \mu_1) \ = d_2 - d_b + \frac{1}{2}(\delta_1 - d_1 + d_b)$; and $\sigma \sim \mathrm{Unif}(0, 2)$, as shown above.

B.5 Prior Assumptions

Incorporating prior belief or knowledge into analysis is a distinctive trait of Bayesian analysis by which more information is used. Quantifying the educated subjective (or 'active') prior belief forms the ground for the informative prior assumption. We performed the analyses under two sets of prior assumptions. First, under a minimum of prior assumptions, an analysis was undertaken using a flat or non-informative prior distribution (which is therefore an objective look at the results based on data alone):

$$\mu_{sb} \sim \mathrm{N}(0, 100^2)$$

$$d_t \sim \mathrm{N}(0, 100^2)$$

with $d_1 = 0$ as an anchor point.

Second, a sceptical analysis was undertaken using an informative prior distribution expressing a subjective belief that there is no difference between any pair of immunosuppressive agents in preserving renal function over time [23]. A normal prior distribution on the log odds parameter was used for this purpose, which is a precise distribution centred at the null, with its precision calculated by mapping the relative treatment effect up to the minimal clinically meaningful OR of 2 (empirically chosen), measured in logarithmic scale. Therefore, the interval between OR = ±2 covers 1.96 SE units of the logarithmic distribution on both sides:

$$\log(\mathrm{OR} = 2) = 0.6931$$

$$\mathrm{SE}_{\log(\mathrm{OR})} = \frac{0.6931 - 0}{1.96}$$

$$= 0.3536$$

therefore, the sceptical prior distribution is specified as:

$$\mu_{sb} \sim N(0, 0.3536^2)$$

$$d_t \sim N(0, 0.3536^2)$$

Different sets of initial values for the stochastic nodes were used to further examine the robustness of results.

References:

[42] Higgins J, Whitehead A. Borrowing strength from external trials in a meta-analysis. Stat Med 1996;15:2733–49.

[43] Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004;23:3105–24.

Appendix C. Consistency Evaluation

An informal test in evaluating consistency between direct and indirect evidence obtained from a comparison network was performed, using the method suggested by Georgia Salanti [44] (URL: http://www.mtm.uoi.gr/index.php/how-to-do-an-mtm/10-how-to-do-an-mtm/18-inconsistency).

There are 4 maintenance treatments analyzed for the outcome of renal failure, and in this analysis 2 closed triangular loops are formed: Aza-Cyclo-MMF and Aza-Cyclo-Pred as shown in Figure 1. Results of the inconsistency evaluation is shown in Table C, where the synthesized mean effect size is measured in the log odds ratio (log OR) scale, with its standard error (SE) given. Between-study variation is measured as heterogeneity Tau^2 using random effects meta-analysis, and Tau^2 measured in this evaluation is assumed to be different for each comparison within each loop, which is estimated using the method of moments estimator for random effects model [44, 45]. In this table, the letter `a' stands for Aza, `c' for Cyclo, `m' for MMF, `p' for prednisone alone; and `acm' stands for the loop Aza-Cyclo-MMF, `acp' for the loop Aza-Cyclo-Pred.

It shows that the Z ratio is rather small with an associated p value rather large for either loop (Table C), thus there is no statistical evidence to reject the null hypothesis of equality between direct and indirect effect sizes. Therefore, consistency can be assumed.

Figure C shows forest plot of the IF (95% confidence interval, CI) calculated for every loop, where no loop's IF appears to be apparently deviant from the null. Each loop in this figure is a closed triangle in the comparison network, where IF is the estimated difference between direct and indirect evidence in this loop. There is no evidence for inconsistency as all of the 95% CIs cover 0, therefore all loops seem to be consistent.

References:

[44] Salanti G, Higgins JPT, Ades AT, Ioannidis JPA. Evaluation of networks of randomized trials. Stat Methods Med Res 2008;17(3):279-301.

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Table C. Inconsistency evaluation for network meta-analysis of maintenance treatments

Loop	Pair	Mean (Log OR)	SE (Log OR)	#Pairs	Tau^2	IF	SE (IF)	Z Ratio	P Value
acm	ac	-0.062	0.659	2	0				
	cm	1.846	1.149	1	0				
	am	0.390	0.506	4	0.0087	1.394	1.417	0.983	0.326
acp	ac	-0.223	0.764	2	0				
	cp	-0.898	1.239	1	0				
	ap	-0.582	0.906	2	0	0.539	1.715	0.315	0.753

Note: Within each loop IF is estimated assuming that each comparison has a specific amount of heterogeneity (Tau^2).

One comparison of a multi-arm study may be removed from a loop to minimize dependence.

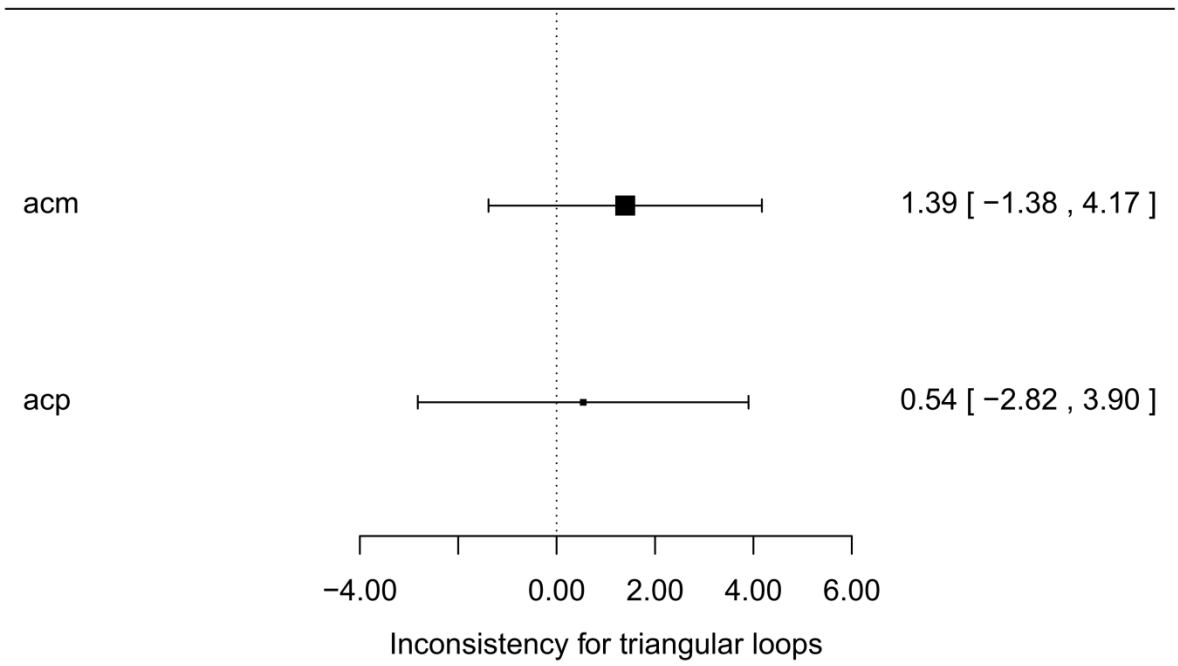

Figure C. Forest plot of the inconsistency factor (IF) estimates with the 95% CI for maintenance treatments for the outcome of renal failure. Within each loop IF is estimated assuming that each comparison has a specific amount of heterogeneity Tau^2. Where the dotted line lies is the value indicated by null hypothesis.

Appendix D. Excluded Studies

The name of the study and reasons for exclusion are shown below.

Abbreviations used are: LN: lupus nephritis; PLN: proliferative lupus nephritis; SLE: systemic lupus erythematosus; CNS: central nervous system; sCr: serum creatinine; RF: renal failure; Cyclo: cyclophosphamide; Aza: azathioprine; MMF: mycophenolate mofetil.

Arends S et al. 2012 [46]: This was a comparison of Cyclo versus Aza and although a long-term study, after 2 years all patients received Aza in both arms. The 2 year outcome data were reported by Grootscholten C et al. 2006 (see below). Therefore redundant.

Austin III HA et al. 1986 [47]: Comparison of Cyclo versus Aza versus prednisone, but patients with Class II nephritis or no biopsy were included (> 27%) and data was given as summary data rather than individual data. Therefore did not meet inclusion criteria for PLN nephritis.

Boletis JN et al. 1999 [48]: The comparison of immunoglobulin versus high-dose Cyclo was not used in any of the other studies. This should be a unique comparison and out of the scope of this meta-analysis.

Boumpas DT et al. 1992 [49]: Comparison of pulse methylprednisolone versus Cyclo in maintenance phase. Primary outcome variable was doubling of serum creatinine for a minimum of one month and if creatinine doubled then patients were allowed to receive Cyclo. Data for renal failure was not analyzable. Therefore did not meet inclusion criteria for primary outcome.

Cade R et al. 1973 [50]: Comparison was prednisone versus Aza but patients were allowed to change treatment during the study. Therefore unable to compare therapy in maintenance phase.

Carette S et al. 1983 [51]: Three arms of prednisone versus Aza versus Cyclo. The primary outcome was doubling of creatinine but individual data on RF was not given. Therefore did not meet inclusion criteria.

Chan TM et al. 2000 [52]: Comparison of MMF versus Cyclo. This was a 12 month study and the data were contained in Chan TM et al. 2005 (this study was included in the meta-analysis). Therefore excluded as redundant.

Chen W et al. 2012 [53]: This was only a 6 month study of tacrolimus versus azathioprine during the maintenance phase and therefore did not meet our eligibility criteria of 12 months as the minimum in maintenance phase.

Dinant HJ et al. 1982 [54]: This was a 6 year study and the outcome data were contained in Steinberg AD et al. 1991 (see below). Therefore redundant.

Donadio JV et al. 1978 [55]: Cyclo was compared to prednisone alone, but Cyclo was only used for 6 months for induction treatment and discontinued afterwards, therefore there were no comparison groups for maintenance treatment.

Fries JF et al. 1973 [56]: Other types of SLE in addition to LN were also included. Therefore the cohort did not meet inclusion criteria.

Fu LW et al. 1998 [57]: Comparison of cyclosporin versus Cyclo. The total study length was 12 months and therefore maintenance phase was 6 months and therefore did not meet inclusion criteria for length of study.

Ginzler EM et al. 1976 [58]: Comparison was prednisone with Aza versus prednisone with Aza and Cyclo, and was a cross-over observational study. This latter therapy is not being used and therefore study was excluded.

Gourley MF et al. 1996 [59]: Comparison of Cyclo versus pulse methylprednisolone but modified at 1 year and therefore maintenance phase was only 6 months which is shorter than 12 months as the minimum as per inclusion criteria.

Grootscholten et al. 2006 [60]: Comparison of Aza versus Cyclo but only for the first 2 years. Following this all patients received Aza. No eligible outcome data was given for these 2 years. Therefore did not meet eligibility criteria.

Hahn BH et al. 1975 [61]: Comparison of prednisone versus Aza. Diseases other than LN, such as CNS lupus, were also included as were patients with Class II LN (> 20%). All results were given as mean. Therefore did not meet inclusion criteria of PLN.

Houssiau et al. 2002, 2004, 2010 [62, 63, 64]: These studies all described the same cohort at differing lengths of follow-up. The comparison was high-dose Cyclo (0.5 g/m^2 – 1.5 g per dose) used for 1 year versus low-dose Cyclo (0.5 g per dose) for 3 months. All patients then received Aza. Therefore the comparison would be Aza versus Cyclo in the maintenance phase. However, as Cyclo was only used for 6 months in the maintenance duration, the length of the study did not meet our eligibility criteria.

Illei GG et al. 2001, 2002 [65, 8]: These 2 studies are of the same patients for differing periods of follow-up time. This was a continuation of Gourley MF et al. 1996. Comparison was pulse methylprednisolone versus Cyclo. However, as described above, therapies could have been modified at 1 year. Therefore did not meet duration of study eligibility criteria.

Klippel JH et al. 1978 [66]: A shorter-term follow-up of study by Dinant HJ et al. 1982 (see above).

Liebling MR et al. 1982 [67]: Methylprednisolone versus placebo was used for 1 year, including an initial induction phase. As there was no comparison to another immunosuppressive therapy and pulse methylprednisolone alone is no longer being used, this study was eliminated.

Lui SE et al. 1997 [68]: Cyclosporine A plus Aza was compared to Cyclo plus Aza for 1 year. As neither of these 2 treatments is being used, this study was eliminated.

Mitwalli AH et al. 2011 [69]: Comparison of 2 doses of Cyclo. Therefore did not meet eligibility criteria as no comparison.

Moroni G et al. 2006 [70]: Comparison of cyclosporine to Aza was used for 2–4 years. The outcome measure was the number of lupus flares and no data for RF were given. Therefore did not meet eligibility criteria.

Petri M et al. 2010 [71]: Comparison of high-dose Cyclo (50 mg/kg per dose) for induction treatment for 4 days versus low-dose Cyclo (750 mg/m^2 per dose) for 6+24 months. No comparator for maintenance treatment. Therefore did not meet eligibility criteria.

Sabry A et al. 2009 [72]: Comparison of high-dose Cyclo (0.5–1 g/m^2 per dose) for 1 year in total including induction versus low-dose Cyclo (0.5 g per dose) used for 3 months followed by Aza. Therefore the comparison was only made for 6–9 months for maintenance treatment which did not meet our eligibility criteria.

Sesso et al. 1994 [73]: Compared Cyclo versus methylprednisolone for maintenance treatment for 9 months without comparison groups afterwards. A 9 month maintenance phase did not meet our eligibility criteria.

Steinberg et al. 1991 [74]: This was the same group of patients followed up at the NIH as reported in Austin III HA et al. 1986, only there was a sub-group analysis.

Sundel et al. 2012 [75]: Comparison of MMF versus Cyclo but was a sub-analysis of adolescents in the ALMS trial. Therefore redundant as data were included in the study by Dooley MA et al. 2011 (included).

Sztejnbok et al. 1971 [76]: General SLE rather than LN patients only.

Yee et al. 2003 [77]: Comparison in maintenance phase was Cyclo with pulse methylprednisolone versus Aza. Rescue treatment was used and the patients receiving this therapy remained in the study and these patients were not indicated in the results. This is the reason this study was eliminated.

Zavada et al. 2010 [78]: Comparison was cyclosporine A versus Cyclo. The outcome measure was response or treatment failure and the number of patients with renal failure was not reported. Therefore did not meet eligibility criteria.

References:

[46] Arends S, Grootscholten C, Derksen RHWM, Berger SP, de Sévaux RGL, Voskuyl AE, et al. Long-term follow-up of a randomised controlled trial of azathioprine/methylprednisolone versus cyclophosphamide in patients with proliferative lupus nephritis. ARD 2012;71:966–73.

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[59] Gourley MF, Austin III HA, Scott D, Yarboro CH, Vaughan EM, Muir J, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis: A randomized, controlled trial. Ann Intern Med 1996;125:549–57.

[60] Grootscholten C, Ligtenberg G, Hagen EC, van den Wall Bake AWL, de Glas-Vos JW, Bijl M, et al. Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. Kidney Int 2006;70:732–42.

[61] Hahn BH, Kantor OS, Osterland CK. Azathioprine plus prednisone compared with prednisone alone in the treatment of systemic lupus erythematosus. Ann Intern Med 1975;83:597–605.

[62] Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido EdR, Danieli MG, et al. Immunosuppressive therapy in lupus nephritis: The Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum 2002;46:2121–31.

[63] Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido EdR, Danieli MG, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: Lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. Arthritis Rheum 2004;50:3934–40.

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[65] Illei GG, Austin HA, Crane M, Collins L, Gourley MF, Yarboro CH, et al., Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. Ann Intern Med 2001;135:248–57.

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[67] Liebling MR, McLaughlin K, Boonsue S, Kasdin J, Barnett EV. Monthly pulses of methylprednisolone in SLE nephritis. J Rheumatol 1982;9:543–8.

[68] Lui SF, Cheng IKP, Tong KL, Li CS, Wong KC, Chan TM, et al. Treatment of type IV lupus nephritis (LN) - comparison of 2 triple therapy regimens: Cyclosporin A (CSA), prednisolone (Pred), azathioprine (Aza) vs. oral cyclophosphamide (POCP), prednisolone, azathioprine. Nephrology 1997;3:S476.

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[77] Yee CS, Gordon C, Dostal C, Petera P, Dadoniene J, Griffiths B, et al. EULAR randomised controlled trial of pulse cyclophosphamide and methylprednisolone versus continuous cyclophosphamide and prednisolone followed by azathioprine and prednisolone in lupus nephritis. ARD 2003;63:525–9.

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Appendix E. Funnel Plot for Detecting Publication Bias

Figure E presents the funnel plot of the included studies.

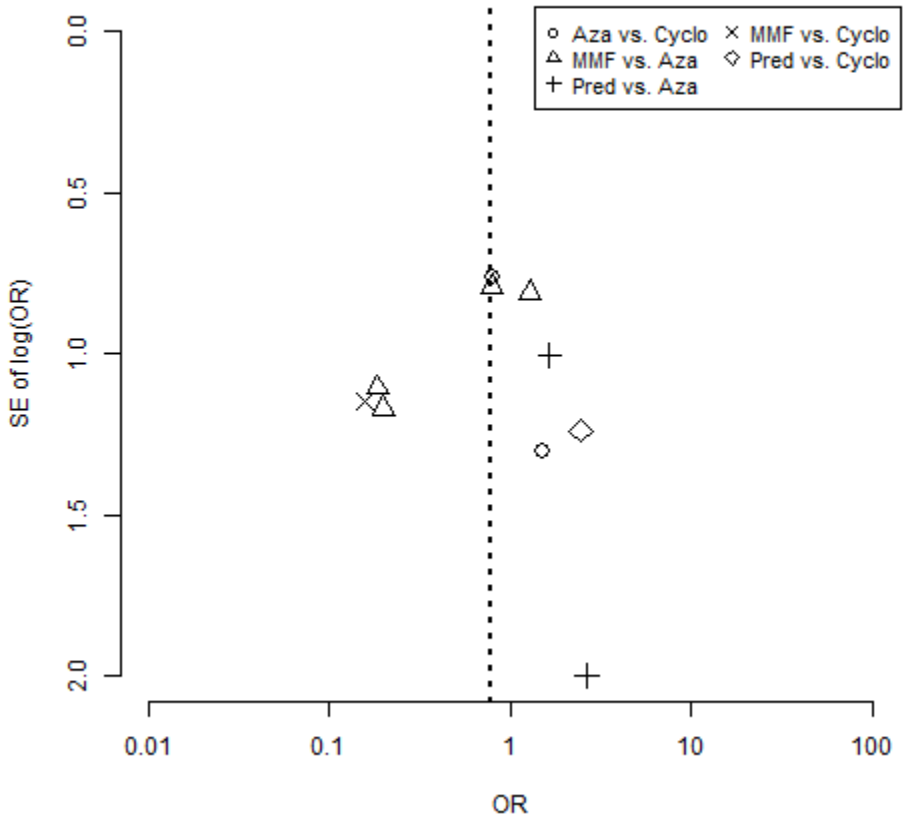

Figure E. Funnel plot of the 6 studies included. It shows that the published results in general are clustered symmetrically around the null, especially for a larger sample size, where SE is small, which indicates that publication bias may not be a serious concern. Abbreviations used: Aza: azathioprine; Cyclo: cyclophosphamide; MMF: mycophenolate mofetil; Pred: prednisone alone.

Appendix F. Caterpillar Plot of the Bayesian Network Meta-analysis

Figure F presents the caterpillar plot of results using Bayesian network meta-analysis.

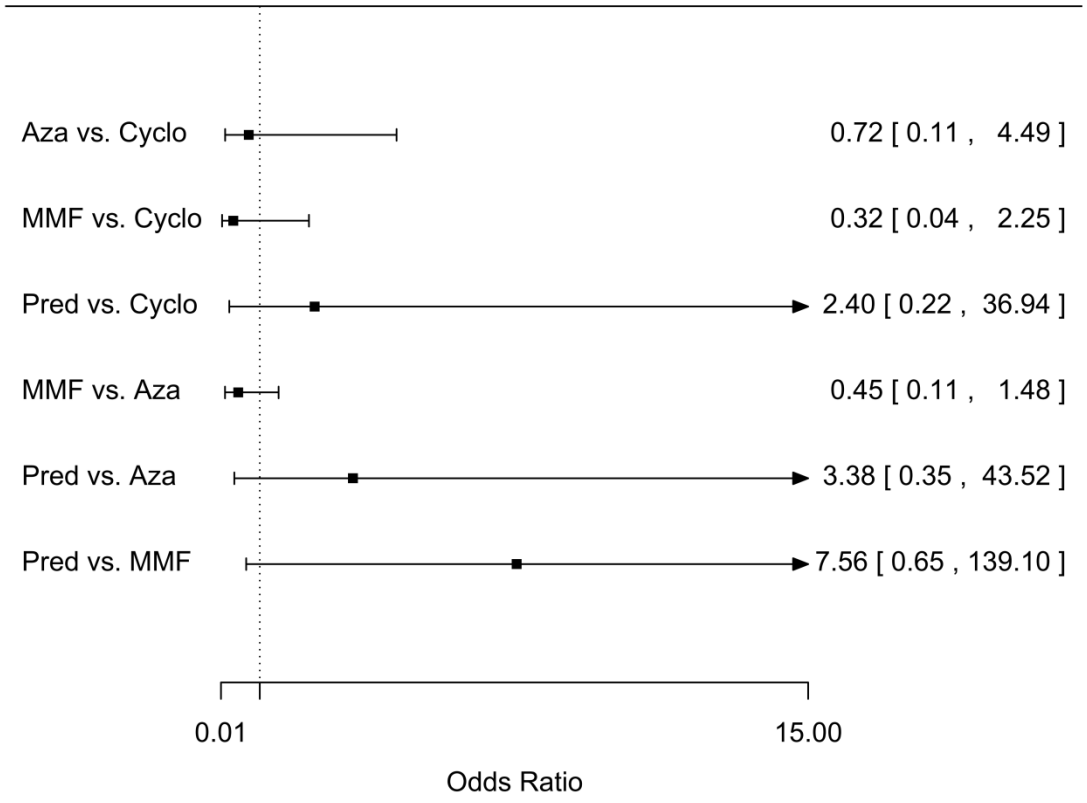

Figure F. Caterpillar plot of the Bayesian network meta-analysis (see also Table 3) - Odds ratio of renal failure at 2 years associated with each of the pairwise comparisons between immunosuppressive agents. The dotted line indicates where OR=1 is. Abbreviations used: Aza: azathioprine; Cyclo: cyclophosphamide; MMF: mycophenolate mofetil; Tac: tacrolimus; Pred: prednisone alone.