Treatments for Lupus Nephritis: A Systematic Review and Network Metaanalysis

Jasvinder A. Singh, Alomgir Hossain, Ahmed Kotb, Ana Oliveira, Amy S. Mudano, Jennifer Grossman, Kevin Winthrop, and George A. Wells

ABSTRACT. ***Objective.*** To compare benefits and harms of lupus nephritis (LN) induction and maintenance treatments.

Methods. We performed a systematic review and Bayesian network metaanalyses of randomized controlled trials (RCT) of immunosuppressive drugs or corticosteroids (CS) in LN. OR and 95% credible intervals (CrI) were calculated.

Results. There were 65 RCT that met inclusion and exclusion criteria. Significantly lower risk of endstage renal disease (ESRD; 17 studies) was seen with cyclophosphamide (CYC; OR 0.49, 95% CrI 0.25–0.92) or CYC + azathioprine (AZA; OR 0.18, 95% CrI 0.05–0.57) compared with standard-dose CS, and with high-dose (HD) CYC (OR 0.16, 95% CrI 0.03–0.61) or CYC + AZA (OR 0.10, 95% CrI 0.03–0.34) compared with HD CS. HD CS was associated with higher risk of ESRD compared with CYC (OR 3.59, 95% CrI 1.30–9.86), AZA (OR 2.93, 95% CrI 1.08–8.10), or mycophenolate mofetil (MMF; OR 7.05, 95% CrI 1.66–31.91). Compared with CS, a significantly higher proportion of patients had renal response (14 studies) when treated with CYC (OR 1.98, 95% CrI 1.13–3.52), MMF (OR 2.42, 95% CrI 1.27–4.74), or tacrolimus (TAC; OR 4.20, 95% CrI 1.29–13.68). No differences were noted for the risk of malignancy (15 studies). The risk of herpes zoster (17 studies) was as follows: OR (95% CrI) MMF versus CS 4.38 (1.02–23.87), CYC versus CS 6.64 (1.97–25.71), TAC versus CS 9.11 (1.13–70.99), and CYC + AZA versus CS 8.46 (1.99–43.61).

Conclusion. Renal benefits and the risk of herpes zoster were higher for immunosuppressive drugs versus CS. Data on relative and absolute differences are now available, which can be incorporated into patient-physician discussions related to systemic lupus erythematosus medication use. (First Release September 1 2016; J Rheumatol 2016;43:1801–15; doi:10.3899/jrheum.160041)

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One-third of all patients with systemic lupus erythematosus (SLE) initially present with nephritis and 50%–60% develop nephritis during the first 10 years[1,2]. Lupus nephritis (LN) accounts for 2% of all endstage renal disease (ESRD) in the United States[3]. It leads to premature death and the overall survival is 88% at 10 years[4,5,6,7].

Immunosuppressive drugs, such as mycophenolate mofetil (MMF), cyclophosphamide (CYC), azathioprine (AZA), etc., improve LN outcomes[8] and are frequently used with corticosteroids (CS)[8]. Because of their efficacy in LN, immunosuppressive drugs also reduce the cumulative CS dose and associated side effects[9,10,11]. They differ from each other in safety during pregnancy, administration route, frequency of dosing, and cost. For example, MMF is contraindicated for use in pregnancy, whereas clinicians consider AZA a safer option[12].

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A major challenge to understanding comparative effectiveness is that few SLE treatments have been compared directly in large head-to-head clinical trials, yet clinicians and patients have to choose among them. It is, therefore, critical to generate comparative effectiveness research (CER) data to compare the effectiveness (and safety) of medications for LN to enable informed decision making. Two common methods for CER are registry/large observational studies examining comparative efficacy and harms (has limitation of various biases, but provides the real-world data) versus examining the data from randomized controlled trials (RCT) with new approaches that can perform indirect comparisons (has limitation of short followup, but has no/minimal biases). These approaches complement each other in uncovering new knowledge, and often confirm or refute anecdotal observations made by clinicians and provide a higher evidence level for clinical observations by individual practitioner. Patients and physicians can use this information related to comparative risks/benefits in medication decision making based on their values, preferences, knowledge, and risk averseness.

The 2012 American College of Rheumatology (ACR) LN treatment guidelines literature review[8] and the Cochrane systematic review of interventions for LN[13] assessed literature up to 2010 and 2012, respectively. Neither performed indirect comparisons. A recent network metaanalysis (NMA) was focused only on the comparative effectiveness of 4 treatments for the maintenance phase and analyzed only 6 studies[14]. Therefore, evidence synthesis using methods to obtain indirect comparisons of efficacy/harms, such as an NMA, is needed. This may uncover new knowledge, as noted previously[15,16,17]. We aimed to perform a comprehensive NMA and systematic review for both induction and maintenance treatments for LN. Our main study objective was to examine randomized trials to assess comparative efficacy and harms of immunosuppressive drugs and CS in LN, incorporating indirect comparisons of treatments using the NMA. Our study, funded by the Patient-centered Outcomes Research Institute (PCORI), provided critical knowledge to build an SLE guide and is currently being tested in a trial.

MATERIALS AND METHODS

We used rigorous methods for the systematic review and NMA based on the Agency for Healthcare Research and Quality recommendations[18], the Cochrane handbook[19], and the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines[20]. The Institutional Review Board at the University of Alabama at Birmingham approved the study.

Criteria for considering studies for systematic review. We included RCT or controlled clinical trials for LN published in English that contained CS or immunosuppressive drugs such as CYC, MMF, AZA, cyclosporine (CSA), tacrolimus (TAC), or rituximab (RTX), and reported any safety or efficacy outcome. Belimumab studies could not be included in our systematic review because these studies included patients with active SLE, most excluding active LN. A Cochrane systematic review of belimumab for SLE is under way[21]. We had multiple prespecified sources of data as detailed below. There were no restrictions with regard to dosage or duration of intervention, i.e., the medication intake. We updated 2 systematic reviews[8,13] with efficacy and safety data from their search end dates (January 2010 and April 2012, respectively) to September 2013.

ACR LN guidelines systematic review[8]. We used the raw data abstracted for this review up to January 2010. An expert librarian (JJ) searched the OVID Medline database from January 2010 (last date for the systematic review for the 2012 ACR LN treatment guidelines) to September 2013. The study protocol was registered in the PROSPERO database: CRD42016032965 (www.crd.york.ac.uk/PROSPERO).

Cochrane library systematic review on treatments of LN[13]. We abstracted the data from the Review Manager (RevMan) tables of the Cochrane Systematic Review that included studies up to April 2012. An experienced Cochrane librarian (TR) conducted a search using the search strategy from the Cochrane review from April 2012 to September 2013 in OVID Medline. The PICO (Patient, Intervention, Comparator, Outcome) were defined as follows:

P: Patients were adults 18 years or older, meeting the 1987 ACR classification criteria for SLE[22].

I: Interventions were immunosuppressant alone or in combination with other immunosuppressant or biologics. Medication doses were categorized as low, standard, or high dose (LD, SD, and HD; Supplementary Data 1, available online at jrheum.org).

C: Placebo or another immunosuppressive drug with/without biologic or CS.

O: Efficacy and safety outcomes (as follows):

Efficacy. Efficacy was assessed with 4 key outcomes (for detailed definitions, see Supplementary Data 1, available online at jrheum.org). ESRD and renal response were the 2 main efficacy outcomes. We also assessed renal relapse[12] and renal failure [doubling of creatinine or decrease in glomerular filtration rate (GFR) > 20%] as secondary efficacy outcomes.

Safety/harms. Malignancy and herpes zoster were the main harm outcomes. We chose these outcomes because patients commonly worry about and ask about the risk of infection and cancer with SLE treatments during treatment decision making. Other harms we assessed were gastrointestinal (GI) side effects (GI upset, diarrhea, etc.), nausea, alopecia, mycobacterial infections, hyperglycemia/diabetes, avascular necrosis/osteonecrosis, mortality, amenorrhea, cytopenia, and urinary bladder toxicity (including hemorrhagic cystitis and hematuria).

We considered using harms data related to CS and immunosuppressive drugs from any SLE RCT, not just from an LN RCT, to have a larger sample. Our *a priori* assumption was that most treatment-related harms did not depend much on whether kidneys were currently involved by SLE; an approach similar to another published NMA of harms[15]. A librarian (CH) performed a search for all SLE trials (excluding LN) in OVID Medline and SCOPUS from inception to February 2014. Examination of the data from this search revealed little additive data for harms for most outcomes of interest (16 RCT, but most had no usable data). Given the added limitation of study population heterogeneity, we determined that the advantages of including these data were outweighed by the disadvantages. Therefore, these data were not included in our analyses.

Two trained abstractors (research associate, data programmer) independently reviewed abstracts and titles in duplicate (AO, AB), discussed to resolve disagreements, and performed consensus. An adjudicator (JS) resolved any disagreements not resolved by consensus. All data were abstracted by 2 independent abstractors (AO, AB) directly into Microsoft Excel sheets. Two reviewers abstracted risk of bias (AO, JS) according to the Cochrane risk of bias tool[23]. We examined each of the following domains as low, high, or unclear risk of bias: randomization sequence generation, allocation sequence concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data (primary outcome data reporting, dropout rates and reasons for withdrawal, appropriate imputation of missing data, an overall completion rate ≥ 80%), and selective outcome reporting and other potential threats to validity (relevant use of co-interventions, bias because of funding source). An unclear risk of bias was designated when there was a lack of information or uncertainty about potential for bias.

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An adjudicator (JS) resolved any disagreements not resolved by consensus. An expert rheumatologist (JS) and an expert in SLE (JG) examined for similarity of studies (study population and interventions) prior to performing evidence synthesis.

Methods for the Bayesian NMA. Bayesian-mixed treatment comparison (MTC) metaanalyses[24,25,26] were conducted to assess comparative effectiveness of various immunosuppressive drugs compared with each other and with CS, corresponding to the main treatment decision points in patients with LN. When not specified, medication dose is the SD.

WinBUGS software (MRC Biostatistics Unit) was used to conduct Bayesian MTC metaanalysis using a binomial likelihood model that allows for the use of multiarm trials[27,28]. Random-effects NMA were conducted; Ohlssen, *et al* outlined the Bayesian fixed- and random-effects models for NMA approaches when considering safety outcomes and the rarity often associated with such outcomes[29]. Assessment of model fit and choice of model was based on the assessment of the deviance information criterion and comparison of residual deviance to number of unconstrained data points[27,30].

Point estimates (OR and relative risk) and 95% credible intervals (CrI) for OR were derived using Markov Chain Monte Carlo methods. Vague priors, such as n ($0–100^2$), were assigned the basic variables identifying the treatment contrasts throughout[27] and informative priors (prior = 0.292) for the variance variable were based on Turner, *et al*[31]. We assumed a common between-study variance for all treatment contrasts for each of the outcomes. To ensure that convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed[32]. Three chains were fit in WinBUGS for each analysis, with 40,000 iterations, and a burn-in of 40,000 iterations[32,33].

Both MTC and traditional metaanalysis require studies to be sufficiently similar to pool their results. To further investigate heterogeneity, where warranted, subgroup analyses and metaregressions[28,34] were considered. We examined consistency-inconsistency plots for evidence of inconsistency, and chose the appropriate model for our analyses. Model diagnostics including trace plots and the Brooks-Gelman-Rubin statistic were assessed to ensure model convergence[27,32]. Graphical aids, in the form of network diagrams, were considered for NMA. Our main analysis combined data from all LN trials (induction, maintenance, and induction and maintenance), as per an *a priori* decision to maximize power for our analysis. We also performed a subgroup analysis for efficacy outcomes by induction trial phase (maintenance phase studies were too few to perform meaningful analysis), because efficacy may differ by induction versus maintenance phases.

RESULTS

Study characteristics. We identified a total of 65 studies that met inclusion and exclusion criteria[12,35–44,45–54,55–64,65–74,75–84,85–94,95,96,97,98] (Table 1; Supplementary Data 2, available online at jrheum.org). Number of studies and patients for each outcome are shown in Table 2. The characteristics of included trials (demographic and treatment of this patient population) and risk of bias are shown in Table 1 and Supplementary Table 1 (available online at jrheum.org). Most studies compared regimens for treatment induction or induction and maintenance (88%) and few compared maintenance regimens only (12%). Sample size ranged from 10–370. Of these studies, 37% were published in 2000 or before, 32% were conducted in the United States, and 43% were multicenter. Included trials studied SLE treatments such as CYC, MMF, AZA, calcineurin inhibitors (CSA, TAC), RTX, CS, plasmapheresis, and leflunomide.

The overall risks of bias of all studies included in our systematic review were as follows: randomization sequence generation: high 5%, low 56%, unclear 39%; allocation sequence concealment: high 3%, low 38%, unclear 61%; blinding of outcome assessors/physician: high 18%, low 59%, unclear 22%; blinding of participants: high 16%, low 54%, unclear 29%; incomplete outcome data: high 13%, low 57%, unclear 29%; selective outcome reporting: high 8%, low 44%, unclear 47%; and funding bias: high 3%, low 33%, unclear 64%. Crude event rates for outcomes assessed are provided in Supplementary Table 2 (available online at jrheum.org). Several outcomes were rare (event rate 5% or lower mostly), including amenorrhea, mycobacterial infections, nausea, etc. (Supplementary Table 2, available online at jrheum.org).

Systematic review and NMA. The results of the systematic reviews provided the data to construct evidence networks for each outcome, using statistical modeling of drug comparisons using NMA (indirect evidence). An exemplar of an evidence network is provided in Figure 1 for ESRD, a key efficacy outcome. NMA results, for each of the evidence network considered, are summarized below and detailed in Table 3, Table 4, Table 5, Table 6, and Supplementary Tables 3–10 and Supplementary Figures 1–4 (available online at jrheum.org). The SD is implicit by the mention of the drug name only; HD and LD are specified in each case, where doses other than SD were used.

We assessed 4 *a priori* defined renal benefits, summarized below, including prevention of ESRD and renal response (primary benefit/efficacy outcomes), and prevention of renal relapse and deterioration of kidney function (secondary benefit/efficacy outcomes; Supplementary Data 1, available online at jrheum.org).

ESRD. Thirteen 2-arm, two 3-arm, and two 4-arm trials (1388 patients) provided data. Most RCT included MMF (n = 6), CYC (n = 9), AZA (n = 9), or CS (n = 6). Significantly lower risk of ESRD were seen in the following groups compared with SD CS: (1) CYC (OR 0.49, 95% CrI 0.25–0.92) or CYC + AZA (OR 0.18, 95% CrI 0.05–0.57) compared with CS; (2) HD CYC compared with HD CS (OR 0.16, 95% CrI 0.03–0.61); and (3) CYC + AZA compared with HD CS (OR 0.10, 95% CrI 0.03–0.34). HD CS was associated with higher risk of ESRD compared with CYC (OR 3.59, 95% CrI 1.30–9.86), AZA (OR 2.93, 95% CrI 1.08–8.10), and MMF (OR 7.05, 95% CrI 1.66–31.91; Table 3). Importantly, no significant between-immunosuppressive drug (CYC, MMF, TAC, AZA, etc.) differences were noted.

Renal response (including stable kidney function). Twelve 2-arm studies and two 3-arm studies (1290 patients) provided data. Most studies included CYC (n = 14), CS (n = 5), or MMF (n = 8). Compared with CS, a significantly higher proportion of patients had renal response when treated with CYC (OR 1.98, 95% CrI 1.13–3.52), MMF (OR 2.42, 95% CrI 1.27–4.74), or TAC (OR 4.20, 95% CrI 1.29–13.68; Table 4). No significant differences were noted between immunosuppressive drugs.

Renal relapse. Fourteen 2-arm studies and two 3-arm studies

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Table 1. Characteristics of included studies.

No.	Studies	Induction/Maintenance	Country	Setting	Study Design	n	Treatment Group: M vs F, or % F, or Total n
1	Austin, *et al*[35]	Induction	USA	NIH	RCT	42	CS: M/F: 3/12, IV CYC: M/F: 3/12, CSA: M/F: 1/11
2	Carette, *et al*[36]	Induction and maintenance	USA	NIH	RCT	53	CS: M/F: 3/12, AZA: M/F: 2/18, CYC: M/F: 5/13
3	Steinberg and Steinberg[37]	Followup	USA	NIH	RCT	111	CS: n = 30, AZA: n = 20, PO CYC: n = 18, IV CYC: n = 20, AZA + CYC: n = 23
4	Donadio, *et al*[38]	Induction	USA	Single center	RCT	39	CS: n = 20, CYC + CS: n = 19
5	Pohl, *et al*[39]	Induction, followup	USA	Multicenter	RCT	86	Standard group: 84.8% F, PLASMA group: 82.5% F
6	Mok, *et al*[40]	Induction and maintenance	Hong Kong	2 hospital sites	RCT	43	IV pulse CYC: M/F: 1/21, pulse CYC followed by AZA: M/F: 1/20
7	Hu, *et al*[41]	Induction	China	Single center	RCT	46	MMF group: 19 F, CYC group: 19 F
8	Wang, *et al*[42]	Induction	China	Single center	RCT	20	MMF group: n = 9, CYC group: n = 11
9	Isenberg, *et al*[43]	Induction	Multinational	Multicenter	RCT	370	Induction therapy: M/F: 57/313, maintenance therapy: M/F: 32/195
10	Radhakrishnan, *et al*[44]	Induction pooled data	USA/multinational	Multicenter, 2 RCT	Pooled analysis of 2 large RCT	84	US study: M/F: 4/20, ALMS study subgroup: M/F: 17/43
11	Wang, *et al*[45]	Induction	China	Multicenter	RCT	110	LEF: M/F: 10/60, CYC: M/F: 3/37
12	Appel, *et al*[46]	Induction and maintenance	Multinational	NIH trial, multicenter	RCT, open-label, parallel-group	370	Induction therapy: M/F: 57/313, maintenance therapy: M/F: 32/195
13	Austin, *et al*[47]	Induction	USA	NIH trials, multicenter	RCT, open-label	107	M/F: 15/92
14	Balletta, *et al*[48]	Induction	Italy	NS	RCT	10	CS: M/F: 1/4, CS + CSA: M/F: 0/5
15	Bao, *et al*[49]	Induction	China	Single center	RCT, open-label	40	MMF + TAC + CS: M/F: 4/16, IV CYC: M/F: 2/18
16	Barron, *et al*[50]	Induction	USA	Single center	Quasi-RCT	22	Oral HD CS: M/F: 2/13, IV pulse CS, then PO CS: M/F: 1/6
17	Boumpas, *et al*[51]	Induction	USA	NS	RCT	65	Pulse CS: M/F: 1/24, pulse CYC: M/F: 3/17, pulse CYC, then quarterly: M/F: 1/19
18	Cade, *et al*[52]	Induction	USA	Teaching hospital	Quasi-RCT	54	HD CS: M/F: 3/12, AZA: M/F: 1/12, AZA + CS: M/F: 3/10, AZA + heparin: M/F: 6/7
19	Chan, *et al*[53]	Induction and maintenance	Hong Kong	Multicenter	RCT	42	CS + MMF: M/F: 6/26, CS + CYC, then CS + AZA: M/F: 4/26
20	Chen, *et al*[54]	Induction	China	Multicenter	RCT	81	CS + TAC: M/F: 5/37, CS + CYC: M/F: 7/32
21	Clark, *et al*[55]	Induction	Canada	Outpatient	RCT	12	Conventional therapy: n = 6, conventional therapy + PLASMA: n = 6
22	Clark, *et al*[56]	Induction	Canada and West Indies	Multicenter	RCT	39	Conventional therapy: M/F: 1/19, conventional therapy + PLASMA: M/F: 5/15
23	Contreras, *et al*[57]	Maintenance	USA	Single center	RCT, open-label	59	IV CYC: M/F: 1/19, AZA: M/F: 2/18, MMF: M/F: 1/19
24	Zavada, *et al*[58]	Induction and maintenance	European countries	Multicenter	RCT, open-label	40	CYC: M/F: 6/15, CSA: M/F: 5/14
25	Derksen, *et al*[59]	Induction	the Netherlands	Multicenter	RCT	20	AZA or CYC: M/F 3/8, PLASMA: M/F: 2/7
26	Donadio, *et al*[60]	Induction	USA	NS	RCT	16	M/F: 2/14, CS vs CS + AZA
27	Donadio, *et al*[61]	Induction	USA	Single center	RCT, open-label	26	CS: M/F: 4/22, CS + CYC: M/F: 5/19
28	Doria, *et al*[62]	Induction	Italy	Single center	RCT	18	M/F: 2/16, std therapy vs std therapy + PLASMA vs std therapy + CS
29	Dyadyk, *et al*[63]	Induction	Ukraine	NS	RCT	59	M/F: 9/50, PO CYC: M/F: 4/17, PO AZA: M/F: 5/33
30	El-Shafey, *et al*[64]	Induction	Egypt	Single center	RCT, open-label	47	MMF: M/F: 1/23, IV pulse CYC: M/F: 1/22
31	Fu, *et al*[65]	Maintenance	Taiwan	Single center	RCT	40	CYC: n = 20, CS + CSA: n = 20
32	Ginzler, *et al*[66]	Induction	USA	Single center	RCT, open-label, noninferiority	140	MMF: M/F: 10/61, CYC: M/F: 4/65
33	Gourley, *et al*[67]	Induction	USA	Single center	RCT	82	CS: M/F: 5/22, CYC: M/F: 6/21, CYC + CS: M/F: 3/25
34	Grootscholten, *et al*[68]	Induction and maintenance	the Netherlands	Multicenter	RCT	87	CYC + CS: M/F: 6/44, AZA + CS: M/F: 9/28
35	Hahn, *et al*[69]	Induction	USA	Single center	RCT	20	CS: M/F: 2/11, AZA: M/F: 2/9
36	Hong, *et al*[70]	Induction	China	NS	RCT	25	Not available
37	Houssiau, *et al*[71]	Induction and maintenance	European	Multicenter	RCT	90	HD IV CYC followed by AZA: M/F: 3/43, LD IV CYC followed by AZA: M/F: 3/41

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Table 1. Continued.

No.	Studies	Induction/Maintenance	Country	Setting	Study Design	n	Treatment Group: M vs F, or % F, or Total n
38	Lewis, *et al*[72]	Induction	USA	Multicenter	RCT	86	CYC + CS: M/F: 7/33, CYC + CS + PLASMA: M/F: 7/39
39	Li, *et al*[73]	Induction	Hong Kong	Single center	RCT	19	RTX: M/F: 9/9, RTX + IV CYC : M/F: 1/9
40	Li, *et al*[74]	Induction	China	NS	RCT, open-label	60	MMF: M/F: 3/17 TAC: M/F: 3/17 CYC: M/F: 2/18
41	Lui, *et al*[75]	Induction	Hong Kong	NS	RCT	34	Not available CSA + CS + AZA vs PO CYC + CS + AZA
42	Rovin, *et al*[76]	Induction	Multinational	NIH trials, multicenter	RCT	144	Std therapy + Placebo: M/F: 5/67 std therapy + RTX: M/F: 9/63
43	Houssiau, *et al*[12]	Maintenance	European	Multicenter	RCT	105	AZA: M/F: 4/48 MMF: M/F: 5/48
44	Mitwalli, *et al*[77]	Induction and maintenance	Saudi Arabia	Single center	RCT	117	HD CYC: M/F: 12/6 1LD CYC: M/F: 5/39
45	Mok, *et al*[78]	Induction	Hong Kong, China	NS	RCT	109	M/F: 11/98 MMF vs TAC
46	Moroni, *et al*[79]	Maintenance	Italy	Multicenter	RCT	69	CSA: M/F: 3/33 AZA: M/F: 4/29
47	Mulic-Basic, *et al*[80]	Induction	Bosnia-Herzegovina	NS	RCT	45	MMF, N = 20 CYC, N = 25
48	Jayne and Zeher[81]	Induction	Multinational	Multicenter	RCT, open-label	81	Not available
49	Ong, *et al*[82]	Induction	Malaysia	Multicenter	RCT, open-label	54	MMF: M/F: 3/23 IV CYC: M/F: 4/15
50	Sabry, *et al*[83]	Induction	Egypt	Single center	Quasi-RCT	46	HD CYC: M/F: 4/22 LD CYC: M/F: 2/18
51	Sesso, *et al*[84]	Induction	Brazil	Single center	RCT	29	IV CYC: M/F: 2/12 IV CS : M/F: 2/13
52	Steinberg, *et al*[85]	Induction	USA	Single center	RCT	15	IV CYC + CS: M/F: 0/7 Placebo + CS: M/F: 0/6
53	Sundel and Lisk[86]	Induction	Multinational	Multicenter	RCT	24	M/F: 5/19 MMF vs IV CYC
54	Wallace, *et al*[87]	Induction	Multinational	Multicenter	RCT	19	Std therapy: M/F: 1/8 std therapy + PLASMA: M/F: 0/9
55	Yee, *et al*[88]	Induction and maintenance	European	Multicenter	RCT, open-label	32	Pulse CYC: M/F: 2/11 Continuous PO CYC followed by PO AZA: M/F: 2/14
56	Li, *et al*[89]	Induction	China	Single center	RCT	60	MMF: M/F: 3/17, TAC: M/F: 3/17, IV CYC: M/F: 2/18
57	Yap, *et al*[90]	Induction	Hong Kong, China	Multicenter	RCT	16	CS + MMF: M/F: 2/5, CS + TAC: M/F: 4/5
58	Stoenoiu, *et al*[91]	Maintenance	Europe	Multicenter	RCT	30	M:F: 1/29
59	Chen, *et al*[92]	Maintenance	China	Multicenter	RCT	70	TAC: M/F: 2/5, 5/29, AZA group: M/F: 2/5, 4/32
60	Arends, *et al*[93]	Induction	the Netherlands	Multicenter	RCT	87	CYC + CS: M/F: 6/44, AZA + CS: M/F: 9/28
61	Sundel, *et al*[94]	Induction	Multinational	Multicenter	RCT	370	Induction, adults: MMF: M/F: 25/150, AZA: M/F: 27/144, Maintenance, adults: MMF: M/F: 15/93, AZA: M/F: 14/89
62	Walsh, *et al*[95]	Induction	Multinational	Multicenter	RCT, posthoc analysis	32	CYC: M/F: 2/10, MMF: M/F: 2/18
63	Petri, *et al*[96]	Induction and maintenance	USA	2 hospital sites	RCT	51	SD CYC: M/F: 3/23, HD CYC: M/F: 2/19
64	Zeher, *et al*[97]	Induction and maintenance	Multinational	Multicenter	RCT	81	SD CS: M/F: 37/42, LD CS: M/F: 29/39
65	Dooley, *et al*[98]	Maintenance	UK	Single center	RCT	227	MMF: M/F: 99/116, AZA: M/F: 96/111

M: male; F: female; NIH: US National Institutes of Health; RCT: randomized controlled trial; NS: not specified; CS: corticosteroids; IV: intravenous; CYC: cyclophosphamide; CSA: cyclosporine; AZA: azathioprine; PO: oral; PLASMA: plasmapheresis; MMF: mycophenolate mofetil; ALMS: the Aspreva Lupus Management Study; LEF: leflunomide; TAC: tacrolimus; HD: high dose; std: standard; LD: low dose; SD: std dose (when dose is not specified, SD should be inferred).

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Table 2. No. studies and patients included for each outcome of interest. Major outcomes are in bold face.

Outcome	Studies	Patients
Endstage renal disease	17	1388
Renal response, including stable kidney function	12	1290
Renal relapse	14	627
Deterioration of kidney function	13	993
Malignancy	14	1128
Herpes zoster	17	1423
Gastrointestinal side effects	**13**	**1526**
Alopecia	**5**	**751**
Nausea	**5**	**717**
Diabetes/hyperglycemia	**6**	**670**
Avascular necrosis/osteonecrosis	**2**	**129**
Mortality	**30**	**6565**
Mycobacterial infections	**2**	**554**
Amenorrhea	**2**	**180**
Urinary bladder toxicity	**2**	**79**
Cytopenia	**4**	**584**

(627 patients) provided data and mostly included CS (n = 2), AZA (n = 6), MMF (n = 4), and CYC (n = 4). Compared with CS, MMF and CYC (SD and LD combined) were associated with lower odds, 0.16 and 0.23, respectively, and compared with AZA, MMF was associated with lower odds of 0.43 of renal relapse (Supplementary Table 3, available online at jrheum.org).

Deterioration of kidney function (doubling of serum creatinine or decrease in GFR > 20%). Thirteen 2-arm and two 3-arm studies (993 patients) provided data. HD CYC was associated with lower odds of deterioration of kidney function compared with SD or HD CS, AZA, or plasmapheresis, ranging from 0.10 to 0.29 (Supplementary Table 4, available online at jrheum.org).

Malignancy. Fourteen 2-arm studies and one 3-arm study (1128 patients) provided data. Studies included AZA (n = 5), MMF (n = 4), CYC (n = 4), or CS (n = 2). No significant between-treatment differences were noted (Table 5). Most

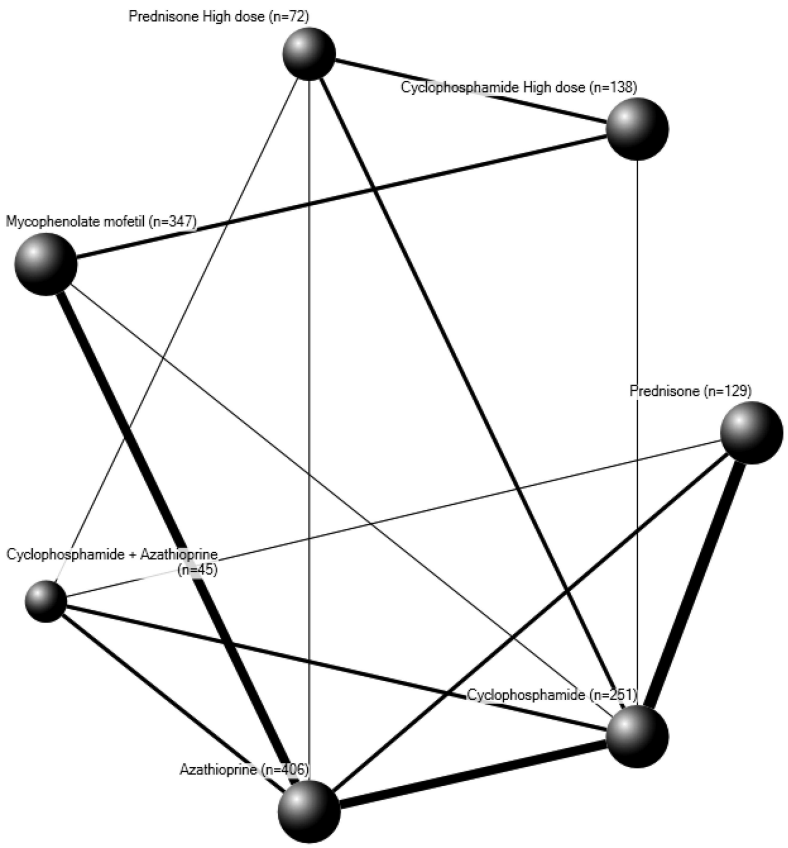

Figure 1. Evidence network for endstage renal disease. The width of lines for each connection in the evidence network is proportional to the number of randomized controlled trials comparing each pair of treatments. The size of each treatment node is proportional to the number of randomized participants (sample size). The number of patients exposed to each respective treatment is shown next to each treatment.

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Table 3. Endstage renal disease: OR, RR, and RD for all treatment comparisons using the random-effects model. Estimates are derived from random effects, Bayesian network metaanalysis, which treats between-study variance as an informative prior (log normal distribution). The similarity of residual deviance for a random-effects model compared with the fixed-effects model shows the robustness of our finding.

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
CYC	CS	**0.49 (0.25–0.92)**	**0.56 (0.33–0.93)**	**–0.12 (–0.22 to –0.01)**
AZA		0.60 (0.26–1.36)	0.67 (0.33–1.26)	–0.09 (–0.21 to 0.06)
MMF		0.25 (0.06–1.04)	0.31 (0.08–1.03)	–0.18 (–0.29 to 0.01)
CS HD		1.74 (0.57–5.34)	1.45 (0.65–2.63)	0.12 (–0.10 to 0.39)
CYC HD		0.27 (0.05–1.24)	0.34 (0.07–1.17)	–0.17 (–0.29 to 0.04)
CYC + AZA, combined		**0.18 (0.05–0.57)**	**0.23 (0.07–0.64)**	**–0.20 (–0.30 to –0.08)**
AZA	CYC	1.23 (0.58–2.60)	1.19 (0.63–2.15)	0.03 (–0.07 to 0.15)
MMF		0.51 (0.12–2.01)	0.55 (0.14–1.76)	–0.06 (–0.16 to 0.11)
CS HD		**3.59 (1.30–9.86)**	**2.56 (1.24–4.58)**	**0.24 (0.04–0.48)**
CYC HD		0.57 (0.12–2.42)	0.61 (0.13–2.01)	–0.06 (–0.16 to 0.14)
CYC + AZA, combined		0.37 (0.11–1.07)	0.41 (0.13–1.06)	–0.09 (–0.17 to 0.01)
MMF	AZA	0.42 (0.11–1.51)	0.47 (0.13–1.39)	–0.09 (–0.21 to 0.06)
CS HD		**2.93 (1.08–8.10)**	**2.15 (1.06–4.10)**	**0.21 (0.01–0.44)**
CYC HD		0.46 (0.10–1.96)	0.51 (0.12–1.70)	–0.08 (–0.21 to 0.11)
CYC + AZA, combined		0.31 (0.09–0.90)	0.35 (0.11–0.91)	–0.11 (–0.24 to –0.01)
CS HD	MMF	**7.05 (1.66–31.91)**	**4.54 (1.45–17.31)**	**0.29 (0.08–0.54)**
CYC HD		1.10 (0.23–5.44)	1.09 (0.26–4.50)	0.01 (–0.14 to 0.19)
CYC + AZA, combined		0.73 (0.13–3.91)	0.75 (0.16–3.61)	–0.02 (–0.19 to 0.09)
CYC HD	CS HD	**0.16 (0.03–0.61)**	**0.24 (0.06–0.71)**	**–0.28 (–0.52 to –0.08)**
CYC + AZA, combined		0.10 (0.03–0.34)	0.16 (0.05–0.43)	**–0.32 (–0.57 to –0.12)**
CYC + AZA, combined	CYC HD	0.66 (0.11–3.99)	0.68 (0.14–3.68)	–0.03 (–0.23 to 0.08)
Random-effect model	Residual deviance		38.07 vs 40 data points	
	Deviance information criteria		158.328	
Fixed-effect model	Residual deviance		38.38 vs 40 data points	
	Deviance information criteria		157.739	
Total patients, n			1343	
Total studies, n			40	
2-arm, n			36	
3-arm, n			2	
4-arm, n			2	

HD CS was defined as one of the following: (1) PRED or methylprednisolone 1 gm/m^2 QD IV × 3 at entry, and then 1 dose IV Q month for 1 year, and (2) PRED 1 mg/kg PO daily with a slow taper up to 1 year. CS use was defined as one of the following: (1) PRED 40 mg PO QOD for 8 weeks, and then taper to 10 mg QD within a year, and (2) 60 mg QD for 1–3 months reduced to 20 mg/day by 6 months. CYC, SD: IV CYC 0.5–1.0 gm/m^2 Q2 month for 1 year or CYC 1–4 mg/kg daily for 3–4 years. HD CYC: IV CYC 0.5–1.0 gm/m^2 Q month × 6–9 months, PO and then Q3 months for 0.5–4 years or PO CYC 10 mg/kg daily. HD LEF was LEF at 1 mg/kg QD × 3 days, and then 30 mg QD × 6 months. Significant data are in bold face. RR: relative risk; RD: risk difference; CrI: credible interval; CYC: cyclophosphamide; AZA: azathioprine; MMF: mycophenolate mofetil; CS: corticosteroids; HD: high-dose; PRED: prednisone; QD: once daily; IV: intravenous; Q month: once every month; PO: oral; QOD: every other day; SD: standard dose; Q2: every 2; Q3: every 3; LEF: leflunomide.

induction RCT were 6 months in duration, and induction and maintenance RCT were 1.5- to 2-years long.

Herpes zoster. Seventeen studies provided data: fifteen 2-arm and 1 each of 3- and 4-arm studies (1423 patients). Studies included AZA (n = 4), MMF (n = 9), CYC (n = 4), or CS (n = 3). Compared with SD CS, several immunosuppressive drugs were associated with higher odds of herpes zoster: MMF 4.4, CYC 6.6, TAC 9.1, and CYC + AZA 8.5, respectively (Table 6).

Other harms. Details of number of studies and treatments compared for other harms are provided in Supplementary Tables 5–10 and Supplementary Figures 1–4 (available online at jrheum.org). In NMA, HD CYC was associated with significantly higher odds of the following: (1) GI side effects: versus MMF, 3.3× higher odds, and versus TAC, 8.2× higher odds (Supplementary Table 5, available online at jrheum.org); and (2) alopecia: versus MMF, 4.5× higher odds (Supplementary Table 6, available online at jrheum.org). No significant between-treatment differences were noted for odds of nausea (Supplementary Table 7, available online at jrheum.org), diabetes/hyperglycemia (Supplementary Table 8), avascular necrosis/osteonecrosis (Supplementary Table 9), and mortality (Supplementary Table 10).

For 4 outcomes, data were available only for comparison of 2 treatments, and therefore only traditional metaanalyses could be performed. We noted the following differences: (1) mycobacterial infections: MMF versus HD CYC, 7.5× higher odds (Supplementary Figure 1, available online at jrheum.org); (2) amenorrhea: MMF versus CYC (HD and LD combined owing to few data), OR 0.17 (Supplementary Figure 2); (3) urinary bladder toxicity (hemorrhagic cystitis/hematuria): CYC versus CS, OR 9.7 (Supplementary Figure 3); and (4)

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Table 4. Renal response: OR, RR, and RD for all treatment comparisons using the random-effects model. Estimates are derived from random-effects, Bayesian network metaanalysis, which treats between-study variance as an informative prior (log normal distribution). The similarity of residual deviance for random-effects model compared with the fixed-effects model shows the robustness of our finding. Data are based on comparisons of each treatment with prednisone or other immunosuppressive drugs.

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% Crl)
CYC	CS	**1.98 (1.13–3.52)**	**1.25 (1.04–1.54)**	**0.15 (0.03–0.27)**
MMF		**2.42 (1.27–4.74)**	**1.31 (1.08–1.62)**	**0.18 (0.05–0.31)**
TAC		**4.20 (1.29–13.68)**	**1.44 (1.09–1.79)**	**0.26 (0.06–0.40)**
AZA		1.09 (0.32–3.79)	1.03 (0.56–1.50)	0.02 (–0.27 to 0.27)
MMF	CYC	1.21 (0.89–1.74)	1.05 (0.97–1.13)	0.03 (–0.02 to 0.09)
TAC		2.10 (0.75–6.23)	1.15 (0.92–1.32)	0.11 (–0.06 to 0.22)
AZA		0.55 (0.17–1.86)	0.83 (0.46–1.15)	–0.13 (–0.41 to 0.11)
TAC	MMF	1.72 (0.60–5.18)	1.10 (0.88–1.28)	0.08 (–0.10 to 0.20)
AZA		0.45 (0.13–1.57)	0.79 (0.44–1.10)	–0.16 (–0.44 to 0.08)
AZA	TAC	0.26 (0.05–1.26)	0.72 (0.40–1.05)	–0.24 (–0.53 to 0.04)
Random-effect model	Residual deviance		24.67 vs 30 data points	
	Deviance information criteria		153.145	
Fixed-effect model	Residual deviance		24.6 vs 30 data points	
	Deviance information criteria		151.748	
Total patients, n			1290	
Total studies, n			14	
2-arm, n			12	
3-arm, n			2	

Significant data are in bold face. RR: relative risk; RD: risk difference; CrI: credible interval; CYC: cyclophosphamide; MMF: mycophenolate mofetil; TAC: tacrolimus; AZA: azathioprine; CS: corticosteroids.

Table 5. Malignancy: OR, RR, and RD for all treatment comparisons using the random-effects model. Estimates are derived from random-effects, Bayesian network metaanalysis, which treats between-study variance as an informative prior (log normal distribution). The similarity of residual deviance for random-effects model compared with the fixed-effects model shows the robustness of our finding.

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% Crl)
MMF	AZA	0.19 (0.02–1.08)	0.20 (0.02–1.08)	–0.01 (–0.03 to 0.00)
CYC, SD or HD		0.32 (0.05–1.79)	0.33 (0.05–1.77)	–0.01 (–0.03 to 0.01)
CS		0.24 (0.00–3.02)	0.24 (0.00–2.94)	–0.01 (–0.03 to 0.03)
CYC, SD or HD	MMF	1.68 (0.29–12.33)	1.68 (0.29–12.14)	0.00 (–0.01 to 0.02)
CS		1.21 (0.02–24.24)	1.21 (0.02–23.37)	0.00 (–0.01 to 0.04)
CS	CYC, SD or HD	0.73 (0.02–9.28)	0.73 (0.02–8.97)	0.00 (–0.02 to 0.04)
Random-effect model	Residual deviance		16.28 vs 15 data points	
	Deviance information criteria		50.439	
Fixed-effect model	Residual deviance		16.61 vs 15 data points	
	Deviance information criteria		50.503	
Total patients, n			1128	
Total studies, n			15	
2-arm, n			14	
3-arm, n			1	

HD PRED was defined as one of the following: (1) PRED or methylprednisolone 1 gm/m^2 QD IV × 3 at entry, and then 1 dose IV Q month for 1 year, and (2) PRED 1 mg/kg PO daily with a slow taper up to 1 year. PRED was defined as one of the following: (1) PRED 40 mg PO QOD for 8 weeks, and then taper to 10 mg QD within a year, and (2) 60 mg QD for 1–3 months reduced to 20 mg/day by 6 months (SD). CYC, SD: IV CYC 0.5–1.0 gm/m^2 Q2 month for 1 year or PO CYC 1–4 mg/kg daily for 3–4 years. HD CYC: IV CYC 0.5–1.0 gm/m^2 Q month × 6–9 months, and then Q3 months for 0.5–4 years or PO CYC 10 mg/kg daily. HD LEF was LEF at 1 mg/kg QD × 3 days, and then 30 mg QD × 6 months. RR: relative risk; RD: risk difference; CrI: credible interval; MMF: mycophenolate mofetil; CYC: cyclophosphamide; SD: standard dose; HD: high dose; CS: corticosteroids; AZA: azathioprine; PRED: prednisone; QD: once daily; IV: intravenous; Q month: once every month; PO: oral; QOD: every other day; Q2: every 2; Q3: every 3; LEF: leflunomide.

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Table 6. Herpes zoster: OR, RR, and RD for all treatment comparisons using the random-effects model. Estimates are derived from random-effects, Bayesian network metaanalysis, which treats between-study variance as an informative prior (log normal distribution). The similarity of residual deviance for random-effects model compared with the fixed-effects model shows the robustness of our finding.

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% Crl)
MMF	CS	**4.38 (1.02–23.87)**	**3.53 (1.01–13.93)**	**16.41 (0.14–45.54)**
CYC		**6.64 (1.97–25.71)**	**4.77 (1.76–15.28)**	**24.68 (7.75–46.17)**
AZA		3.21 (0.79–14.55)	2.77 (0.81–10.41)	11.54 (–2.03 to 32.09)
TAC		**9.11 (1.13–70.99)**	**5.71 (1.12–21.29)**	**31.49 (1.00–72.68)**
CYC LD		2.92 (0.44–23.72)	2.57 (0.46–12.98)	9.92 (–5.40 to 46.77)
CYC HD		3.87 (0.84–22.88)	3.21 (0.86–13.33)	14.24 (–1.44 to 45.43)
LEF HD		4.73 (0.52–50.87)	3.73 (0.55–17.89)	17.43 (–4.13 to 66.57)
CYC + AZA		**8.46 (1.99–43.61)**	**5.54 (1.78–19.06)**	**30.10 (7.37–60.42)**
CYC	MMF	1.51 (0.40–5.38)	1.34 (0.55–3.64)	7.69 (–19.49 to 30.43)
AZA		0.73 (0.23–2.16)	0.78 (0.33–1.87)	–4.82 (–27.82 to 11.61)
TAC		2.01 (0.29–14.37)	1.58 (0.39–5.06)	13.63 (–20.88 to 55.34)
CYC LD		0.66 (0.17–2.46)	0.72 (0.22–1.86)	–5.74 (–25.63 to 18.27)
CYC HD		0.88 (0.46–1.84)	0.91 (0.54–1.56)	–2.00 (–13.73 to 11.78)
LEF HD		1.05 (0.21–6.23)	1.04 (0.26–2.98)	0.82 (–21.65 to 39.62)
CYC + AZA		1.92 (0.48–7.93)	1.55 (0.61–4.30)	12.65 (–15.03 to 41.73)
AZA	CYC	0.49 (0.13–1.73)	0.59 (0.21–1.50)	–12.68 (–36.26 to 10.19)
TAC		1.35 (0.25–7.29)	1.21 (0.34–2.66)	6.54 (–22.57 to 43.94)
CYC LD		0.44 (0.08–2.67)	0.54 (0.12–1.85)	–13.78 (–37.98 to 21.18)
CYC HD		0.59 (0.15–2.48)	0.68 (0.22–1.82)	–9.71 (–32.67 to 19.47)
LEF HD		0.70 (0.09–6.14)	0.78 (0.14–2.65)	–6.67 (–34.88 to 40.70)
CYC + AZA		1.28 (0.36–4.90)	1.17 (0.48–2.64)	5.29 (–20.65 to 35.44)
TAC	AZA	2.79 (0.37–20.31)	2.04 (0.45–6.53)	19.19 (–14.19 to 60.88)
CYC LD		0.90 (0.18–4.53)	0.92 (0.22–2.97)	–1.33 (–20.01 to 29.46)
CYC HD		1.21 (0.37–4.40)	1.16 (0.44–3.04)	2.80 (–14.38 to 28.19)
LEF HD		1.44 (0.22–11.68)	1.32 (0.27–4.67)	5.59 (–17.83 to 51.19)
CYC + AZA		2.65 (0.67–10.99)	1.99 (0.74–5.49)	18.10 (–6.89 to 47.20)
CYC LD	TAC	0.32 (0.03–3.41)	0.46 (0.09–2.47)	–19.48 (–62.91 to 21.60)
CYC HD		0.44 (0.06–3.46)	0.57 (0.16–2.56)	–15.74 (–57.57 to 21.10)
LEF HD		0.52 (0.04–7.53)	0.66 (0.11–3.64)	–12.09 (–57.96 to 40.90)
CYC + AZA		0.96 (0.13–7.56)	0.97 (0.33–4.23)	–1.00 (–45.12 to 39.07)
CYC HD	CYC LD	1.34 (0.39–4.93)	1.25 (0.51–3.93)	3.80 (–18.20 to 23.34)
LEF HD		1.61 (0.24–12.75)	1.42 (0.31–6.27)	6.46 (–22.19 to 48.39)
CYC + AZA		2.92 (0.49–18.24)	2.14 (0.64–9.84)	18.62 (–14.69 to 49.07)
LEF HD	CYC HD	1.19 (0.27–6.00)	1.14 (0.33–3.02)	2.72 (–17.80 to 38.82)
CYC + AZA		2.18 (0.52–8.96)	1.71 (0.65–4.96)	14.64 (–12.95 to 42.62)
CYC + AZA	LEF HD	1.83 (0.21–14.33)	1.49 (0.42–7.99)	11.39 (–34.65 to 45.37)
Random-effect model	Residual deviance		38.65 vs 37 data points	
	Deviance information criteria		167.538	
Fixed-effect model	Residual deviance		41.1 vs 37 data points	
	Deviance information criteria		168.295	
Total patients, n			1423	
Total studies, n			17	
2-arm, n			15	
3-arm, n			1	
4-arm, n			1	

HD PRED was defined as one of the following: (1) PRED or methylprednisolone 1 gm/m^2 QD IV × 3 at entry, and then 1 dose IV Q month for 1 year, and (2) PRED 1 mg/kg PO daily with a slow taper up to 1 year. PRED was defined as one of the following: (1) PRED 40 mg PO QOD for 8 weeks, and then taper to 10 mg QD within a year, and (2) 60 mg QD for 1–3 months reduced to 20 mg/day by 6 months (SD). LD CYC: IV CYC 500 mg Q 14 days × 6 doses. CYC, SD: IV CYC 0.5–1.0 gm/m^2 Q2 month for 1 year or PO CYC 1–4 mg/kg daily for 3–4 years. HD CYC: IV CYC 0.5–1.0 gm/m^2 Q month × 6–9 months, and then Q3 months for 0.5–4 years or PO CYC 10 mg/kg daily. HD LEF was LEF at 1 mg/kg QD × 3 days, and then 30 mg QD × 6 months. Significant data are in bold face. RR: relative risk; RD: risk difference; CrI: credible interval; MMF: mycophenolate mofetil; CYC: cyclophosphamide; AZA: azathioprine; TAC: tacrolimus; SD: standard dose; LD: low dose (when not specified, SD should be inferred); HD: high dose; LEF: leflunomide; CS: corticosteroids; PRED: prednisone; QD: once daily; IV: intravenous; Q month: once every month; PO: oral; QOD: every other day; Q2: every 2; Q3: every 3.

cytopenia: HD CYC versus MMF, higher odds of 1.69 (Supplementary Figure 4). When the consistency assumption could be evaluated, we did not find any evidence of inconsistency in the NMA for various outcomes after examining the consistency-inconsistency plots (Supplementary Figure 5, available online at jrheum.org).

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Subgroup analysis for induction treatment trials. Nine 2-arm, one 3-arm, and two 4-arm trials (890 patients) provided ESRD data. Findings were similar to the overall analysis. Significantly lower risks of ESRD were seen in the following groups compared with SD CS: (1) CYC (OR 0.47, 95% CrI 0.25–0.92) or CYC + AZA (OR 0.20, 95% CrI 0.05–0.68) compared with CS; (2) HD CS compared with CYC (OR 4.83, 95% CrI 1.55–16.11) and AZA (OR 3.46, 95% CrI 1.08–12.15); and (3) CYC + AZA compared with HD CS (OR 0.09, 95% CrI 0.02–0.33; Supplementary Table 11, available online at jrheum.org). Importantly, no significant between–immunosuppressive drug (CYC, MMF, TAC, AZA, etc.) differences were noted.

Renal response (including stable kidney function). Eleven 2-arm studies and two 3-arm studies (920 patients) provided data. Compared with CS, a significantly higher proportion of patients had renal response when treated with CYC (OR 2.01, 95% CrI 1.10–3.64), MMF (OR 2.74, 95% CrI 1.31–5.91), or TAC (OR 4.33, 95% CrI 1.24–15.25; Supplementary Table 12, available online at jrheum.org). No significant differences were noted between immunosuppressive drugs.

Renal relapse. Three 2-arm studies (145 patients) provided data. Compared with CS and AZA, CYC (SD and LD combined) were associated with lower odds of renal relapse, with OR 0.15 (95% CrI 0.03–0.70) and 0.19 (95% CrI 0.04–0.76), respectively (Supplementary Table 13, available online at jrheum.org).

Deterioration of kidney function (doubling of serum creatinine or decrease in GFR > 20%). Nine 2-arm and two 3-arm studies (669 patients) provided data. HD CYC was associated with lower odds of deterioration of kidney function compared with SD or HD CS, with OR 0.29 (95% CrI 0.08–0.97) and 0.10 (95% CrI 0.01–0.84), respectively (Supplementary Table 14, available online at jrheum.org).

Risk and benefit of treatments compared with each other. Table 7 shows a staircase diagram comparing CS to common/standard immunosuppressive doses and combinations of immunosuppressive drugs, another way to depict the results of NMA for 2 outcomes. A side-by-side comparison of odds can be made between treatments using this approach. There were no significant differences between treatments, except for significantly lower odds of ESRD with CYC compared with CS (Table 7). For example, CYC use was significantly less likely (0.49 times) than CS to be associated with ESRD, but not significantly different regarding the risk of malignancy.

DISCUSSION

To our knowledge, ours is one of the first comprehensive systematic reviews, metaanalyses, and NMA of immunosuppressive drugs and CS for the treatment of LN. We noted differences in the efficacy and the harms of various treatments. By incorporating indirect and direct comparisons in the NMA, we present a comprehensive assessment of comparative benefits and harms of LN treatments. We noted no differences in the risk of malignancy, diabetes/hyperglycemia, osteonecrosis, nausea, and mortality among immunosuppressive drugs. About half of the studies had a low risk of bias on the Cochrane risk of bias tool. It is just as important to pay attention to the lack of differences among immunosuppressive drugs as to significant differences.

The 4- to 9-fold higher risk of herpes zoster with various immunosuppressive drugs compared with CS is the first quantification of the risk of herpes zoster with immunosuppressive drugs in patients with LN, to our knowledge. The 17 included studies had patients with mean age ranging 29 years to 36 years followed for 6 months to 7 years (8 studies lasting 6 mos). Thus, these very young patients with LN are at high risk of herpes zoster, with risk relatively higher than patients with noninflammatory musculoskeletal conditions[99]. Herpes zoster is a potentially preventable disease by the use of a vaccine, and patients with SLE mount a good immune response to this vaccine[100]. Given the availability of a vaccine to prevent herpes zoster, we believe that zoster vaccination should be administered prior to immunosuppressive initiation. The immunosuppressive state in most LN might persuade some clinicians to consider the administration of zoster vaccination in younger patients after evaluating individualized risk-benefit ratio for each patient. At the very

Table 7. Staircase diagram comparing the risk of ESRD (above) versus malignancy (below). Values are OR (95% CrI).

Corticosteroid	0.49 (0.25–0.92)	0.60 (0.26–1.36)	0.25 (0.06–1.04)
1.36 (0.11–1.50)	Cyclophosphamide	1.23 (0.58–2.60)	0.51 (0.12–2.01)
4.17 (0.33–221.3)	3.13 (0.56–20)	Azathioprine	0.42 (0.11–1.51)
0.83 (0.04–50)	0.59 (0.08–3.45)	0.19 (0.02–1.08)	Mycophenolate mofetil

We report only the OR of treatment comparisons common to both outcomes. This diagram is read diagonally from top to bottom with the top treatment always serving as the reference treatment. For instance, the table illustrates that the OR for having ESRD for cyclophosphamide versus corticosteroid is 0.49 (95% CrI 0.25–0.92), which is statistically significant. In this case, corticosteroid is the treatment diagonally above cyclophosphamide, and therefore serves as the reference treatment. Similarly, the OR of cyclophosphamide is 1.36 (95% CrI 0.11–1.50) compared with corticosteroid for having a malignancy, not statistically significant. ESRD: endstage renal disease; CrI: credible interval.

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least, all patients 60 years and older with SLE should be immunized prior to immunosuppression initiation, as per the US Centers for Disease Control and Prevention recommendation for zoster vaccine use in that population[101]; on the other hand, the US Food and Drug Administration packet insert for the vaccine allows it for patients 50 years or older[102].

A recent NMA was focused only on comparative effectiveness of 4 treatments (CYC, AZA, MMF, prednisone vs comparator) for the maintenance phase, and analyzed only 6 studies[14]. The OR (95% CrI) of developing renal failure at 2–3 years was 0.72 (0.11–4.49) for AZA versus CYC, 0.32 (0.04–2.25) for MMF versus CYC, 2.40 (0.22–36.94) for prednisone alone versus CYC, and 0.45 (0.11–1.48) for MMF versus AZA. There was no conclusive evidence of superiority of 1 regimen over another. In another NMA of induction therapies for SLE, there were no differences between CYC, MMF, and TAC for creatinine or proteinuric remission at 6 months[103]. Our NMA differed from these previous NMA in the outcomes examined (benefits and harms) and the approach (induction and maintenance trials combined to get maximum power for comparative efficacy and safety of SLE treatments).

Interestingly, there were no differences among immunosuppressive drugs or the immunosuppressive drugs and CS for the risk of malignancy. The number of studies was few for some comparisons, indicating that the lack of significance may be due to the lack of association, or more likely an insufficient power to detect a small difference. Such a small difference may or may not be clinically meaningful. Importantly, as has been noted in previous similar analyses, it is very difficult to see differences in cancer rates in RCT settings given the short trial duration, because the development of cancers usually takes years. Most induction RCT were 6 months in duration, and induction and maintenance RCT were 1.5- to 2-years long, with very few lasting > 2 years. Thus, the lack of differences should not be interpreted as all treatments imparting equal risk. Well-designed longterm cohort and registry studies are needed to answer this question. Similarly, no risk differences were noted for diabetes/hyperglycemia, osteonecrosis, and mortality; again these are events with low incidence rates and we were underpowered to detect differences.

An important finding was that there was no difference in renal outcomes between immunosuppressive drugs, with 1 exception, i.e., compared with AZA, MMF was associated with lower odds of 0.43 of renal relapse. Both the findings of MMF being superior to AZA and the absence of any other differences in renal outcomes between various immunosuppressive drugs are noteworthy. Because our study aggregated all data, our findings summarize the experience to date. This indicates that several effective treatment options are available for LN. We cannot rule out minor but clinically important differences among these treatments, which may become obvious once more data become available. With the currently available data, MMF is only superior to AZA for the risk of renal relapse.

We found notable differences in the efficacy between CS and immunosuppressive drugs. Significantly lower risk of ESRD were seen in CYC and CYC + AZA compared with CS, with OR of 0.18 to 0.48, and for MMF, CYC, HD CYC, and CYC + AZA compared with HD CS, with OR ranging from 0.10 to 0.28. The higher efficacy of immunosuppressive drugs compared with CS is well recognized and widely published in the literature and reiterated in the 2012 ACR LN treatment guidelines[8]. Our systematic review and NMA advances this knowledge by providing the magnitude of these differences. This evidence emphasizes the importance of immunosuppressive drugs in preventing renal damage in patients with LN. A 2–10× higher risk of ESRD with CS alone compared with most immunosuppressive drugs might be helpful in convincing a skeptical patient, who considers immunosuppressive drugs as a "cancer drug" and might consider using CS alone for the treatment of LN, without realizing the true efficacy of immunosuppressive drugs versus CS. Similar findings were observed for other renal efficacy outcomes. In practice, a combination of immunosuppressive drugs and CS is used for most optimal renal outcomes.

Some side effects differed between immunosuppressive drugs. Both HD CYC and LD CYC were each associated with 17- to 25-fold higher odds of cytopenia than MMF or CSA. This information is very helpful, because it allows for a more informed discussion of benefits/harms prior to the initiation of immunosuppressive drugs. Instead of saying to the patient, "Your risk of low blood counts is higher with CYC than MMF," one can quantify this risk either numerically or qualitatively depending on patient preference [i.e., "the risk is 17- to 25–fold higher" or "the risk is much (or very much) higher"].

CYC was associated with 4.5× higher odds of alopecia as compared with MMF. This information may be particularly helpful during treatment decision making to young patients, especially women, who may be very concerned about hair loss. HD CYC was associated with 3.3× higher odds of GI side effects compared with MMF and 8.2× higher odds compared with TAC. The GI tolerability of an immunosuppressive drug likely contributes to the adherence rates, and seems to be an important harm to keep in mind. Healthcare providers usually address this risk before initiation in most/all patients and during the initial few days to improve the likelihood of continuation of CYC by the use of concomitant antiemetics, if nausea is mild and/or tolerable. CYC was associated with 9.7× higher odds of urinary bladder toxicity (hemorrhagic cystitis/hematuria) compared with CS, which was statistically significant. This is not surprising, because urinary bladder toxicity with the use of CYC is well known.

Our study has other limitations that deserve further

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discussion. Because of the inclusion of short-term RCT with limited person-years exposure, we may have missed harms that are associated with longer-term use. Most NMA and metaanalyses included a small number of patients (usually < 1000), despite combining all the available data. Therefore, we suspect that we may have missed some important differences between various treatments of LN because of low power, i.e., type II error. Another possibility is the lack of differences between these treatments with regards to certain side effects. Our current analysis does not allow us to distinguish these 2 possibilities. Only 50% of the studies included in our systematic review had low risk of bias on various criteria, and the risk of bias was unclear for the majority of the remaining studies. This must be considered while interpreting results from our study. The number of trials and data available for maintenance-only trials was too few, not allowing us to perform a meaningful NMA analysis for this subgroup, in contrast to the subgroup analyses we performed for induction trials. We used a random-effects model, because it may work better than a fixed-effect model for rare events, because it can incorporate informative prior distributions on variables expressing between-study variability.

Multiple comparisons raise the possibility of some comparisons being significant just by chance. However, given the small sample sizes, short followup, and the rarity of most outcomes, type II error (not type I error) is the main study limitation, i.e., we likely missed some real differences due to lack of data, e.g., osteonecrosis risk with CS versus immunosuppressive drugs. In general, it is noted that the NMA has an inflated rate of type I error and a low statistical power in the existence of heterogeneity[104]. Although 2 clinicians examined the studies for clinical heterogeneity prior to study inclusion in NMA and found no evidence of significant heterogeneity, some heterogeneity between patient populations enrolled in the studies may have contributed at least partially to some differences between treatments that we noted in indirect comparisons. When the consistency assumption could be evaluated, we did not find any evidence of inconsistency in the NMA. Because we assumed a common between-study variance for all treatment contrasts for each of the outcomes, if there were substantive heterogeneity of the between-study variances within a network, the priors effect would be a tighter CrI but a similar point estimate.

Our systematic review and NMA found that, for renal outcomes, immunosuppressive drugs were better than CS, both clinically and statistically. No significant between-immunosuppressive drug difference was seen for renal outcomes, except that MMF was better than AZA in preventing renal relapse. We noted significant differences among immunosuppressive drugs and/or CS for herpes zoster, alopecia, GI tolerability, amenorrhea, leukopenia, and urinary bladder toxicity. No differences were noted between various immunosuppressive drugs for several harms, including the risk of cancer, diabetes, osteonecrosis, nausea, and mortality; some lack of differences may be due to rarity of outcomes. Our current study offers a better knowledge of (relative and absolute) comparative efficacy and harms of LN treatments. This knowledge can help patients with the choice of the best medication for them based on their comorbidity profile, childbearing potential, beliefs/values regarding specific harm/s, and preferences. These data were incorporated into a patient-decision aid, which is being tested in a PCORI-funded randomized trial in patients with LN.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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