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Original Investigation

Induction and Maintenance Immunosuppression Treatment of Proliferative Lupus Nephritis: A Network Meta-analysis of Randomized Trials

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Background: Intravenous (IV) cyclophosphamide has been first-line treatment for inducing disease remission in lupus nephritis. The comparative efficacy and toxicity of newer agents such as mycophenolate mofetil (MMF) and calcineurin inhibitors are uncertain.

Study Design: Network meta-analysis.

Setting & Population: Patients with proliferative lupus nephritis.

Selection Criteria for Studies: Randomized trials of immunosuppression to induce or maintain disease remission.

Interventions: IV cyclophosphamide, oral cyclophosphamide, MMF, calcineurin inhibitor, plasma exchange, rituximab, or azathioprine, alone or in combination.

Outcomes: Complete remission, end-stage kidney disease, all-cause mortality, doubling of serum creatinine level, relapse, and adverse events.

Results: 53 studies involving 4,222 participants were eligible. Induction and maintenance treatments were administered for 12 (IQR, 6-84) and 25 (IQR, 12-48) months, respectively. There was no evidence of different effects between therapies on all-cause mortality, doubling of serum creatinine level, or end-stage kidney disease. Compared to IV cyclophosphamide, the most effective treatments to induce remission in moderate- to high-quality evidence were combined MMF and calcineurin inhibitor therapy, calcineurin inhibitors, and MMF (ORs were 2.69 [95% CI, 1.74-4.16], 1.86 [95% CI, 1.05-3.30], and 1.54 [95% CI, 1.04-2.30], respectively). MMF was significantly less likely than IV cyclophosphamide to cause alopecia (OR, 0.21; 95% CI, 0.12-0.36), and MMF combined with calcineurin inhibitor therapy was less likely to cause ovarian failure (OR, 0.25; 95% CI, 0.07-0.93). Regimens generally had similar odds of major infection. MMF was the most effective strategy to maintain remission.

Limitations: Outcome definitions not standardized, short duration of follow-up, and possible confounding by previous or subsequent therapy.

Conclusions: Evidence for induction therapy for lupus nephritis is inconclusive based on treatment effects on all-cause mortality, doubling of serum creatinine level, and end-stage kidney disease. MMF, calcineurin inhibitors, or their combination were most effective for inducing remission compared to IV cyclophosphamide, while conferring similar or lower treatment toxicity. MMF was the most effective maintenance therapy.

INDEX WORDS: Lupus nephritis; immunosuppression; remission; induction therapy; maintenance therapy; mycophenolate mofetil (MMF); intravenous cyclophosphamide; calcineurin inhibitor; end-stage kidney disease (ESKD); dialysis; renal failure; toxicity; adverse events; meta-analysis.

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Systemic lupus erythematosus principally affects women of child-bearing age. Kidney involvement affects 20% to 75% of patients in the first 10 years.[1] Although 5-year survival for patients with systemic lupus erythematosus was <50% in the 1950s, this has improved to >90%, attributed to improved immunosuppression and other medical therapies. Therapies have transformed lupus nephritis from an acute to a chronic illness, in which the longer term efficacy and adverse effects of treatments may assume greater importance in medical decision making.

Intravenous (IV) cyclophosphamide combined with corticosteroids has been first-line therapy to induce remission from lupus nephritis, but it causes considerable toxicity.[2] Existing pairwise meta-analyses suggest similar efficacy for mycophenolate mofetil (MMF) and IV cyclophosphamide with lower toxicity for MMF, but whether MMF or other drugs are equivalent or superior to IV cyclophosphamide for induction and maintenance of disease remission is uncertain.[3,4] However, standard pairwise meta-analysis is only able to compare 2 drug classes that have already been evaluated in head-to-head trials. In a complex condition with several options for treatment, of which some have not been directly compared in trials, a network meta-analysis offers the potential to compare all therapeutic strategies simultaneously within a single framework and rank treatments per efficacy and safety. Network analysis has been used to evaluate induction therapy in lupus nephritis, but results have been inconclusive due to relatively few included studies[5,6] or reporting of drug harms only.[7]

METHODS

Overview

A network meta-analysis was performed within a frequentist framework. The meta-analysis was conducted and reported according to a prespecified protocol (Item S1, available as online supplementary material) and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement.[8] Ethics committee approval was not required for this study design.

Data Sources and Searches

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase were searched on July 20, 2016, using a highly sensitive search strategy without language restriction (Item S1). A Cochrane review and meta-analysis was also screened for eligible randomized trials.[3]

Study Selection

Parallel-group randomized trials involving adults, adolescents, or children 10 years or older with proliferative lupus nephritis and who received immunosuppression to induce or maintain remission were included. Included trials reported comparisons between 2 immunosuppression strategies, placebo, or usual care. Two reviewers (S.C.P. and D.J.T.) independently screened titles and abstracts of retrieved search records to determine potential eligibility. Any potentially eligible citation was reviewed in full text by the same 2 reviewers, who resolved discrepancies through consensus. Potentially eligible articles published in languages other than English were translated before full-text assessment.

Data Extraction

Two investigators (S.C.P. and D.J.T.) abstracted data independently into an electronic database. The authors cross-checked the data and reached consensus for any discrepancies through discussion.

Risk of Bias

Two independent reviewers (S.C.P. and D.J.T.) assessed risks of bias using the Cochrane Collaboration assessment tool.[9]

Data Synthesis and Analysis

The primary outcomes of interest for induction therapy were complete remission and all-cause mortality. Other outcomes were end-stage kidney disease, doubling of serum creatinine level, failure to induce remission, major infection, alopecia, ovarian failure, malignancy, nausea, vomiting, bone toxicity, bladder toxicity, leukopenia, and herpes infection. In maintenance therapy trials, relapse after remission was the primary outcome. Studies reporting zero events in all arms were excluded from analyses. Data from trials principally evaluating induction treatment were analyzed separately from trials evaluating maintenance treatment.

The clinical setting and participant characteristics were evaluated to consider whether the trials were sufficiently similar that a network meta-analysis approach was appropriate.[10] Box plots were generated according to treatment class to explore distributions of key effect modifiers, including age, sex, serum creatinine level, and date of publication. We intended to explore distributions of treatment classes by ethnicity or race, but these assessments were precluded by insufficient data observations.

Random-effects pairwise meta-analysis was then conducted. Heterogeneity of treatment estimates between trials in pairwise meta-analysis was assessed using χ^2 test and the corresponding I^2 statistic. I^2 thresholds of 0% to 40%, 30% to 60%, 50% to 90%, and 75% to 100% were considered to represent heterogeneity that might not be important, that is moderate, that is substantial, and that is considerable, respectively, considering also the magnitude and direction of treatment effects.[11]

Finally, using a frequentist framework, random-effects network meta-analysis was used to compare all classes of immunosuppression for each prespecified outcome.[10,12] We assumed a random-effects model to describe the effects of the base treatment in each study in each network, with the conventional assumption of a normal distribution for random effects. Comparative treatment effects were calculated as odds ratios (ORs) and 95% confidence intervals (CIs). The extent of heterogeneity in each network analysis was evaluated using the restricted maximum likelihood method to generate a common heterogeneity variance (tau [τ]), which was then compared with an empirical distribution of heterogeneity variances, considering the range of ORs expected. Values of 0.1 to 0.5 were considered low, those >0.5 to 1.0 were considered fairly high, and those >1.0 represented fairly extreme heterogeneity.[13] To explore for network inconsistency, a loop-specific approach was used that compares the estimated treatment effects derived from direct and indirect evidence in all triangular and quadratic loops in a network. To check the assumption of consistency in the entire analytical network, the design-by-treatment interaction approach was used.[14]

Drug classes were ranked to generate a hierarchy of treatments for a given clinical end point. The relative ranking probability of each treatment being among the "best" treatment was obtained using surface under the cumulative ranking (SUCRA) curves and displayed using rankograms. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach