Comparative Efficacy and Safety of Tacrolimus, Cyclosporin A, Mycophenolate Mofetil, Cyclophosphamide, and Corticosteroids as Induction Therapy for Membranous Lupus Nephritis: A Network Meta-Analysis

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Keywords
Tacrolimus · Cyclosporin A · Mycophenolate mofetil · Cyclophosphamide · Membranous lupus nephritis

Abstract
Background: There were limited data on randomized controlled trials (RCTs) evaluating the effectiveness and safety of tacrolimus (TAC), cyclosporin A (CSA), mycophenolate mofetil (MMF), cyclophosphamide (CYC), and corticosteroids as induction agents in membranous lupus nephritis, and they were inconclusive. Objectives: This study aimed to assess the relative efficacy and safety TAC, CSA, MMF, CYC, and corticosteroids as induction therapy for membranous lupus nephritis. Method: RCTs examining the efficacy and safety of TAC, CSA, MMF, CYC, and corticosteroids as induction therapy in patients with membranous lupus nephritis were included. We performed a Bayesian random-effects network meta-analysis to combine direct and indirect evidence from the RCTs. Results: Five RCTs comprising 126 patients met the inclusion criteria. TAC and CSA showed a trend toward a higher overall response rate (complete remission plus partial remission) than MMF and CYC. Similarly, MMF and CYC showed a trend toward a higher overall response than corticosteroids. Ranking probability based on the surface under the cumulative ranking curve indicated that TAC had the highest probability of being the best treatment for achieving the overall response, followed by CSA, MMF, CYC, and corticosteroids. In terms of safety, corticosteroids showed the highest probability of decreasing the risk of infections, followed by CSA, CYC, MMF, and TAC. Conclusions: TAC and CSA were the most efficacious induction treatments for patients with membranous lupus nephritis, and corticosteroids had the highest probability of decreasing the risk of infections.

Introduction
Renal involvement occurs in up to 60% of the patients with systemic lupus erythematosus (SLE), with lupus nephritis (LN) being the leading cause of morbidity and mortality [1]. Proliferative glomerulonephritis (classes III and IV according to the International Society of Nephrology/Renal Pathology Society classification) is a severe disease that generally requires intensive therapy to induce remission and avoid substantial renal and overall mortality [2]. Class V LN accounts for 10–15% of all LN cases [3]. In contrast to proliferative lupus glomerulonephritis, membranous LN is associated with a low probability of progression to end-stage renal disease but a significant
risk of thromboembolic consequences [4]. It is often accompanied by nephrotic-range proteinuria, which may result in peripheral edema, infection, and/or hyperlipidemia. Patients with membranous LN are at a high risk of morbidity and mortality from prolonged nephrotic syndrome.

Since membranous LN is less frequent than class III or IV LN, the best treatment for it is unknown. In both the European League Against Rheumatism and the American College of Rheumatology recommendations [5, 6], mycophenolate mofetil (MMF) is recommended as the first-line therapy for membranous LN. However, these suggestions are based on a subgroup analysis of two randomized controlled trials (RCTs) of patients with LN [7, 8]. However, research has shown that newer treatments, such as tacrolimus (TAC), are successful in the treatment of membranous LN, while cyclosporin A (CSA) and cyclophosphamide (CYC) have also been implicated as alternative therapies [8–12].

There were limited data on RCTs evaluating the comparative effectiveness and safety of TAC, CSA, MMF, CYC, and corticosteroids (CS) as induction agents in membranous LN, and they were inconclusive. Network meta-analysis combines direct and indirect evidence of relative treatment effects at the same time [13], allowing for the comparative estimation of effectiveness between multiple interventions by combining evidence from a network of RCTs, even when some comparisons have not been investigated head-to-head [14]. This study compared the effectiveness and safety of TAC, CSA, MMF, CYC, and CS as induction treatments for membranous LN using network meta-analysis.

Methods

Identification of Eligible Studies and Data Extraction

We performed an exhaustive search for studies that examined the efficacy and safety of TAC, CSA, MMF, CYC, and CS in patients with membranous LN. A literature search was performed using PubMed, EMBASE, and the Cochrane Controlled Trials Register to identify available articles (up to July 2021). The following keywords and subject terms were used in the search: “lupus nephritis,” “tacrolimus,” “cyclosporine,” “cyclophosphamide,” and “mycophenolate mofetil.” All article references were reviewed to identify additional studies that were not included in the electronic databases. RCTs were included if the study met the following criteria: (1) compared TAC, CSA, or MMF with CYC or CS or TAC with MMF as induction therapy for membranous LN, (2) provided endpoints for the efficacy and safety of TAC, CSA, MMF, CYC, and CS after induction therapy, and (3) included patients with biopsy-proven class VLN. The exclusion criteria were as follows: (1) inclusion of duplicate data and (2) lack of adequate data for inclusion. The efficacy outcome was the number of patients who achieved renal remission, including complete and partial remission after induction therapy (overall response). Complete and partial remission definitions were based on the remission criteria used in each trial. The safety outcome was the number of patients who were infected. The following information was extracted from each study: first author, year of publication, and kidney biopsy class; the number of patients treated with TAC, CSA, MMF, CYC, and CS; efficacy and safety outcomes of the drugs after induction therapy. We quantified the methodological qualities of the four studies using Jadad scores [15]. Network meta-analysis was conducted in accordance with the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [16].

Evaluation of Statistical Associations for Network Meta-Analysis

The efficacy and safety of TAC, CSA, MMF, CYC, and CS as induction therapy for membranous LN were ordered according to the probability of being ranked as the best performing agent. A random-effects model was used as a conservative method, and a Bayesian network meta-analysis was conducted using NetMetaXL [17] and WinBUGS statistical analysis program version 1.4.3 (MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK). The Markov chain Monte Carlo method was used to obtain pooled effect sizes [18]. All chains were run with 10,000 burn-in iterations, followed by 10,000 monitoring iterations. The information on relative effects was converted to a probability that a treatment was the best, second best, and so on, with the ranking of each treatment (called the surface under the cumulative ranking curve [SUCRA] [19]) expressed as a percentage, ranging between 100% and 0% when a treatment is certain to be the best and the worst, respectively. The summary estimates were presented in league tables by ranking the treatments in order of the most pronounced impact on the outcome under consideration based on SUCRA [19]. We reported the pairwise odds ratio and 95% credible interval adjusted for multiple-arm trials. Pooled results were considered statistically significant if the 95% credible interval did not contain a value of 1.

Test for Inconsistency and Sensitivity Analysis

Inconsistency refers to the extent of disagreement between the direct and indirect evidence [20]. Assessing the inconsistency is important for conducting a network meta-analysis [21]. We plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to assess the network inconsistency between the direct and indirect estimates in each loop [22]. A sensitivity test was performed by comparing the random- and fixed-effects models.

Results

Studies Included in the Meta-Analysis

A total of 819 studies were identified by electronic or manual searches, and 10 were selected for a full-text review based on the title and abstract details. However, 5/10
studies were excluded because they contained duplicate data, non-RCT data, or no outcome data. Thus, five RCTs comprising 126 patients met the inclusion criteria [8–12]. Ten pairwise comparisons were performed, including five direct comparisons and five interventions for the network meta-analysis (Fig. 1). The Jadad scores for all studies except one were 3, indicating high study quality. The relevant features of the studies included in the meta-analysis are presented in Table 1.

**Network Meta-Analysis of the Efficacy of TAC, CSA, MMF, CYC, and CS in RCTs**

We considered the number of overall renal remissions as the efficacy outcome. TAC and CS are listed diagonally in the top left and bottom right of the league tables because they showed the most and least favorable SUCRA results, respectively (Tables 1, 2). TAC and CSA showed a trend toward a higher overall response rate than MMF and CYC (Table 1; Fig. 1). Similarly, MMF and CYC showed a trend toward a higher overall response than CS (Table 1; Fig. 1). Ranking probability based on SUCRA indicated that TAC had the highest
Network Meta-Analysis of the Safety of TAC, CSA, MMF, CYC, and CS in RCTs

The risk of serious infections tended to be lower with CS than CSA, CYC, MMF, and TAC (Table 2; Fig. 2). Ranking probability based on SUCRA indicated that CS had the highest probability of being the safest treatment as they showed a lower risk of serious infections, followed by CSA, CYC, MMF, and TAC (Table 3).

Table 1. Characteristics of individual studies included in the meta-analysis

| Study [Ref.]          | Ethnicity | LN biopsy class | Sample size | Subject numbers | Follow-up period, months |
|-----------------------|-----------|-----------------|-------------|-----------------|--------------------------|
| Ginzler et al. [9]    | Mixed     | V               | 8<sup>a</sup> | NA 5            | 24 weeks                 |
| Appel et al. [10]     | Mixed     | V               | 32<sup>a</sup> | NA 15           | 24 weeks                 |
| Austin et al. [11]    | Mixed     | V               | 42          | NA NA 12        | 48 weeks                 |
| Yap et al. [12]       | Asian     | V               | 16          | 7 NA NA          | 96 weeks                 |
| Mok et al. [13]       | Asian     | V               | 28          | 12 NA NA         | 24 weeks                 |

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TAC, tacrolimus; CSA, cyclosporin A; MMF, mycophenolate mofetil; CYC, cyclophosphamide; CS, corticosteroid.

Table 2. League tables showing the results of the network meta-analyses comparing the effects of all drugs including ORs and 95% CrIs

| A Efficacy. OR >1 means the treatment in top left is better |
|----------------------------------------------------------|
| TAC                                                      |
| 1.22 (0.01–335.57)                                       |
| 2.75 (0.21–58.51)                                        |
| 4.85 (0.13–412.20)                                       |
| 21.48 (0.21–6,082.73)                                     |
| CSA                                                      |
| 2.30 (0.02–173.50)                                       |
| 4.11 (0.14–135.30)                                       |
| 17.88 (0.59–664.89)                                      |
| MMF                                                      |
| 1.72 (0.14–37.58)                                        |
| 7.89 (0.14–753.01)                                       |
| CYC                                                      |
| 4.42 (0.18–116.20)                                       |
| CS                                                       |
| 0.24 (0.01–4.19)                                         |
| 0.16 (0.01–2.85)                                         |
| 0.10 (0.00–5.28)                                         |
| 0.01 (0.00–2.85)                                         |

| B Safety. OR <1 means the treatment in top left is better |
|----------------------------------------------------------|
| CS                                                       |
| 0.24 (0.01–4.19)                                         |
| 0.16 (0.01–2.85)                                         |
| 0.10 (0.00–5.28)                                         |
| 0.01 (0.00–2.85)                                         |
| CSA                                                      |
| 0.68 (0.04–13.37)                                        |
| 0.41 (0.01–24.05)                                       |
| 0.06 (0.00–12.93)                                       |
| MMF                                                      |
| 0.60 (0.04–9.07)                                         |
| 0.09 (0.00–7.04)                                        |
| TAC                                                      |
| 0.15 (0.00–4.52)                                         |

CrI, credible interval; OR, odds ratio; TAC, tacrolimus; CSA, cyclosporin A; MMF, mycophenolate mofetil; CYC, cyclophosphamide; CS, corticosteroid.
of the random- and fixed-effects models provided the same interpretation, indicating that the results of this network meta-analysis are robust (Fig. 1, 2).

**Discussion**

We gathered and evaluated existing data on the relative effectiveness and safety of TAC, CSA, MMF, CYC, and CS as induction treatments in patients with membranous LN in this network meta-analysis. In terms of effectiveness, our findings indicate that TAC and CSA are the most effective drugs for induction therapy in these patients, followed by MMF and CYC, both of which outperformed CS. In terms of safety, CS were the safest medication because they had the greatest likelihood of lowering the risk of infections, followed by immunosuppressants such as CSA, CYC, MMF, and TAC. Patients with steroid-resistant nephropathy were not included in this analysis because all studies in this meta-analysis did not include patients with steroid-resistant nephropathy. Therefore, we could say that there was no effect on the analysis result that TAC was more effective than CS.
Although our network meta-analysis differs from a previous study by Tang et al. [18], we included only RCTs and used Bayesian network meta-analysis to analyze TAC and CSA separately. Our findings are consistent with network meta-analyses which show that CS are associated with reduced infection rates when compared with immunosuppressants [18], although TAC and CSA are preferred over MMF and CYC as induction treatments for membranous LN. As calcineurin inhibitors, TAC and CSA may stabilize the podocyte cytoskeleton by blocking synaptopodin dephosphorylation and degradation, a protein that controls the structure of podocyte foot processes [23]. Proteinuria is often associated with effacement of the podocyte foot process [24]. In accordance with these findings, our data suggested that TAC and CSA were more efficacious than MMF and CYC in patients with membranous LN. Infection is a major cause of morbidity and mortality in patients with SLE [25]. In the present study, we discovered that CS were associated with a lower risk of infection when compared with immunosuppressants; however, statistical significance was not attained. It may be concluded that induction therapy with TAC and CSA is the first choice for patients with membranous LN because many SLE patients are relatively young women, long-term maintenance therapy is required even after the introduction of remission. Regarding safety, we think that CS is safer in respect with infection compared to other immunosuppressants. The conclusion may not change, though the analysis includes studies using three or four of the five drugs, because this analysis was a network meta-analysis using both direct and indirect comparison evidence.

However, our findings should be considered with care because of several shortcomings in our research. First, only a few RCTs with limited sample sizes were included. As a result, more head-to-head trials are required since network meta-analyses cannot replace direct treatment comparisons. Second, the findings of this network meta-analysis may have been influenced by heterogeneity in the design and patient characteristics of the included studies. For example, the response to immunosuppressive drugs for treating LN seems to differ according to ethnicity; however, only a few studies have performed ethnic-specific analyses. Third, this study did not address medication efficacy and safety outcomes completely as it solely focused on their effectiveness and safety, based on the number of patients who obtained an overall response and acquired infections rather than evaluating a range of outcomes. Fourth, it has been reported that the therapeutic effect on LN varies depending on the race. However, it was hard to find any difference in efficacy between races in this analysis because this meta-analysis consisted of 2 Asian studies and 3 mixed ethnicity studies.

Nonetheless, this meta-analysis has several advantages. We could rank the efficacy and safety of immunosuppressants as induction therapy for membranous LN. The number of individuals with membranous LN in the included studies ranged from 8 to 32; however, this pooled analysis included a total of 126 individuals. Unlike the individual studies, we could offer more precise data by improving the statistical power and resolution by combining the findings of different analyses [26–28].

In conclusion, we observed that TAC and CSA were the most efficacious induction treatments for patients with membranous LN, and CS had the highest probability of decreasing the risk of infections in a Bayesian network meta-analysis involving five RCTs comparing TAC, CSA, MMF, CYC, and CS. More research is required to establish the relative effectiveness and safety of TAC, CSA, MMF, CYC, and CS among more patients with membranous LN.

**Statement of Ethics**

Ethical approval was not required for this study in accordance with local/national guidelines.

**Conflicts of Interest Statement**

The authors declare that they have no competing interests.
Immunosuppressants for Membranous Lupus Nephritis

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Author Contributions
Young Ho Lee was involved in conception and design of study, acquisition of data, analysis and/or interpretation of data, drafting the manuscript, and revising the manuscript critically for important intellectual content. Gwan Gyu Song was involved in conception and acquisition of data, analysis and/or interpretation of data, and revising the manuscript critically for important intellectual content.

References
1. Waldman M, Appel GB. Update on the treatment of lupus nephritis. Kidney Int. 2006 Oct; 70(8):1403–12.
2. Neumann K, Wallace DJ, Azen C, Nessim S, Fichman M, Metzger AL, et al. Lupus in the 1980s: III. influence of clinical variables, biopsy, and treatment on the outcome in 150 patients with lupus nephritis seen at a single center. Semin Arthritis Rheum. 1995 Aug; 25(1):47–55.
3. Schieppati A, Remuzzi G, Tognoni G, Cinotti G, D’Amico G, Ponticelli C, et al. Lupus nephritis: prognostic factors and probability of maintaining life-supporting renal function 10 years after the diagnosis. Am J Kidney Dis. 1992;19(5):473–9.
4. Mercadal L, Montcel ST, Nochy D, Queffeuilou L, Piette JC,irsch-Bagnis C, et al. Factors affecting outcome and prognosis in membranous lupus nephropathy. Nephrol Dial Transplant. 2002;17(10):1771–8.
5. Hahn BH, Mcmahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res. 2012;64(6):797–808.
6. Fanouriakis A, Kostopoulou M, Cheema K, Anders HJ, Aringer M, Bajema I, et al. 2019 update of the joint European league against rheumatism and European renal association: European Dialysis and transplant association (EULAR/ERA–EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis. 2020;79(6):713–23.
7. Radhakrishnan J, Moutzouris DA, Ginzler EM, Solomos N, Siempos II, Appel GB. Mycophenolate mofetil and intravenous cyclophosphamide are similar as induction therapy for class V lupus nephritis. Kidney Int. 2010; 77(2):152–60.
8. Yap DY, Yu X, Chen XM, Lu F, Chen N, Li XW, et al. Pilot 24 month study to compare mycophenolate mofetil and cyclosporine in the treatment of membranous lupus nephritis with nephrotic syndrome. Nephrology. 2012; 17(4):352–7.
9. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med. 2005;353(21):2219–28.
10. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol. 2005 May;20(5):1103–12.
11. Austin HA 3rd, Illei GG, Braun MJ, Balow JE. Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. J Am Soc Nephrol. 2009 Apr;20(4):901–11.
12. Mok CC, Ying KY, Yim CW, Siu YP, Tong KH, To CH, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. Ann Rheum Dis. 2016;75(1):30–6.
13. Catalá-López F, Tobias A, Cameron C, Moher D, Hutton B. Network meta-analysis for comparing treatment effects of multiple interventions: an introduction. Rheumatol Int. 2014; 34(11):1489–96.
14. Young Ho L, Gwan Gyu S. Comparative efficacy and safety of seckinumab and adalimumab in patients with active ankylosing spondylitis: a bayesian network meta-analysis. Res Synth Methods. 2020;11(3):251–65.
15. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1–12.
16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339(4):b2535–69.
17. Brown S, Hutton B, Clifford T, Coyle D, Grimshaw M, Wells G, et al. A microsoft-excel-based tool for running and critically appraising network meta-analyses: an overview and application of NetMetaXL. Syst Rev. 2014;3(1):110.
18. Caldwell DM, Aes AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ. 2005;331(7521):897.
19. Salanti G, Aes AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64(2):163–71.
20. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Aes AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making. 2013;33(5):641–56.
21. Higgins J, Jackson D, Barrett J, Lu G, Aes A, White I. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods. 2012;3(2):98–110.
22. Valkenhof G, Lu G, Brock B, Hilleg E, Aes A, Welton NJ. Automating network meta-analysis. Res Synth Methods. 2012;3(4):285–99.
23. Faul C, Donnelly M, Mersch-Gomez S, Chang YH, Franz S, Delfgaauw J, et al. The actin cytoskeleton of kidney podocytes is a direct target of the antiinflammatory effect of cyclosporine A. Nature Med. 2008;14(9):931–8.
24. Kalluri R. Proteinuria with and without renal glomerular podocyte effacement. J Am Soc Nephrol. 2006;17(9):2383–9.
25. Zanmann-Goddard G, Shoenfeld Y, Zandman-Goddard G, Shoenfeld Y. Infections and SLE. Autoimmunity. 2005;38(7):743–85.
26. Lee YH. An overview of meta-analysis for clinicians. Korean J Intern Med. 2018;33(2):277.
27. Lee YH, Song GG. Circulating interleukin-37 levels in rheumatoid arthritis and systemic lupus erythematosus and their correlations with disease activity: a meta-analysis. J Rheum Dis. 2020;27(3):152–8.
28. Lee YH, Song GG. Associations between circulating interleukin-17 levels and systemic lupus erythematosus and between interleukin-17 gene polymorphisms and disease susceptibility: a meta-analysis. J Rheumatic Dis. 2020;27(1):37–44.

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