Immunosuppressive Treatment for Proliferative Lupus Nephritis: Summary of a Cochrane Review

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Systemic lupus erythematosus primarily affects women of child-bearing age and is more common for ethnic minorities, who may experience a more aggressive disease. Kidney involvement affects ~50% of people with systemic lupus erythematosus,[1] leading to end-stage kidney disease (ESKD) for 15% of patients at 10 years.[2] Improved immunosuppression has transformed lupus nephritis, improving 5-year survival from <50% in the 1950s to >90% in the 1990s.[2] As patient and renal survival improve, the longer-term efficacy and adverse effects of therapies may assume greater importance in clinical decision making.

Our previous Cochrane Review published in 2012[3] identified that mycophenolate mofetil (MMF), compared with intravenous cyclophosphamide, may exhibit little or no difference in inducing remission, with lower risks for ovarian failure. MMF was more effective than azathioprine in maintaining remission. A 2017 network meta-analysis, including an additional 15 studies, demonstrated that MMF was more effective in inducing remission compared to intravenous cyclophosphamide, but had a similar risk for ovarian failure.[4] However, there was uncertainty regarding effects on mortality and ESKD due to infrequent events. In the past 5 years, numerous trials have evaluated many biologics and the combination of MMF and tacrolimus for induction therapy in lupus nephritis. Our updated Cochrane Review[5] evaluates the relative effects of all available immunosuppressive therapies for the induction and maintenance treatment of proliferative lupus nephritis. This is a summary of the findings of this latest Cochrane Review.

We searched the Cochrane Kidney and Transplant Registry through March 2, 2018, for randomized controlled trials and quasi–randomized controlled trials of immunosuppressive therapy in patients with biopsy-proven proliferative lupus nephritis. Pairwise random-effects meta-analysis was performed to estimate efficacy and safety. We critically appraised study methodology using the Cochrane Risk of Bias tool and assessed certainty of the evidence using GRADE.[6]

Findings

Seventy-four studies (5,175 participants) were included in this review. There were 67 studies on induction therapy, with a median 12 months' follow-up, and 9 studies on maintenance therapy, with a median 30 months' follow-up.

Induction Therapy With MMF Versus Intravenous Cyclophosphamide

Treatment with MMF, compared with intravenous cyclophosphamide, may lead to little or no difference in complete remission (8 studies, 828 participants, 214 events; relative risk [RR], 1.17 [95% CI, 0.97-1.42]; low-certainty evidence; Fig 1). It is uncertain whether MMF reduces mortality and prevents ESKD compared to intravenous cyclophosphamide because the certainty of the evidence is very low. MMF probably avoids treatment-related alopecia (3 studies, 622 participants, 93 events; RR, 0.29 [95% CI, 0.19-0.46]; moderate-certainty evidence), but incurs diarrhea (3 studies, 569 participants, 103 events; RR, 2.42 [95% CI, 1.64-3.58]; moderate-certainty evidence). However, the comparative risk of MMF and intravenous cyclophosphamide for ovarian failure is uncertain because treatment estimates are fragile and imprecise.

Induction Therapy With MMF Plus Tacrolimus Versus Intravenous Cyclophosphamide

Low-dose MMF combined with tacrolimus may induce disease remission (2 studies, 402 participants, 145 events; RR, 2.38 [95% CI, 1.07-5.30]; low-certainty evidence) and achieve stable kidney function (<20% worsening of serum creatinine; 2 studies, 402 participants, 159 events; RR, 1.78 [95% CI, 1.40-2.26]; low-certainty evidence) to a greater extent than intravenous cyclophosphamide. The comparative safety of these treatment strategies is uncertain because these trials[7,8] largely included patients of Asian ethnicity, and there is substantial imprecision due to sparse data.

Biologic Therapies

The effectiveness and safety of biologics (eg, abatacept, ocrelizumab, rituximab, and sirukumab) is uncertain due to very low-certainty evidence. Information is restricted to a small number of studies with low numbers of events and inconsistent outcome reporting.

Maintenance Therapy

Azathioprine incurs higher risks for disease relapse (4 studies, 452 participants, 94 events; RR, 1.75 [95% CI, 1.20-2.55]; moderate-certainty evidence), doubling of serum creatinine level (RR, 2.19 [95% CI, 1.03-4.66]; low-certainty evidence), and leukopenia (3 studies, 412 participants, 18 events; RR, 5.61 [95% CI, 1.68-18.72]; low-certainty evidence). However, it is uncertain whether

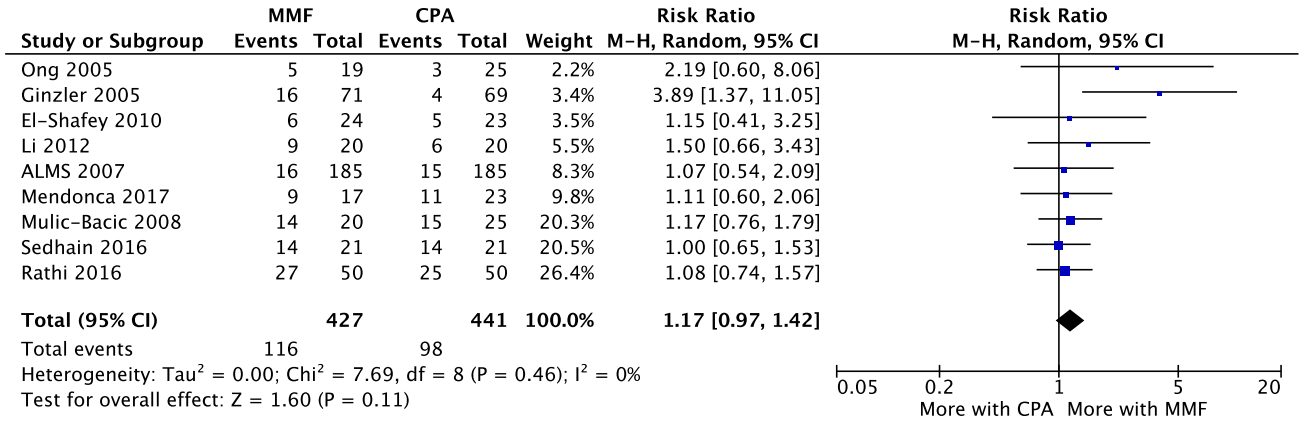

Figure 1. Forest plot of mycophenolate mofetil (MMF) versus intravenous (IV) cyclophosphamide (CPA) complete renal remission. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel. Adapted from Tunnicliffe et al[5] with permission of the copyright holder; original image © 2018 The Cochrane Collaboration and was published by John Wiley & Sons, Ltd.

azathioprine has different effects on mortality or ESKD than MMF because the certainty of the evidence is very low.

Conclusions

MMF provides equivalent disease remission and probably avoids drug-related toxicity compared to intravenous cyclophosphamide, supporting the use of MMF in addition to corticosteroids as first-line induction therapy for proliferative lupus nephritis. MMF is appropriate as first-line maintenance therapy, providing the greatest efficacy for prevention of disease relapse after induction with fewer adverse events.

Lower dose MMF combined with tacrolimus may induce complete remission to a greater extent than intravenous cyclophosphamide. However, the generalizability of these findings may be limited. The safety and effectiveness of biologics is uncertain.

To date, trials evaluating treatment for proliferative lupus nephritis have not been designed to assess mortality and ESKD. Future studies might also address the longer-term outcomes of MMF as maintenance therapy to provide guidance around duration and tapering of therapy.

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