Oral mycophenolate led to more complete remissions than intravenous cyclophosphamide for active lupus nephritis

Ginzler EM, Dooley MA, Aranow C, et al. **Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis.** N Engl J Med. 2005;353:2219-28.

Clinical impact ratings: Allerg & Immunol ★★★★★★☆ Nephrology ★★★★★★★

QUESTION

In patients with active lupus nephritis, is oral mycophenolate mofetil (MMF) plus corticosteroids noninferior to intravenous cyclophosphamide (IVC) plus corticosteroids for inducing remission?

METHODS

Design: Randomized, controlled, noninferiority trial.
Allocation: {Concealed}†.*
Blinding: Unblinded.*
Follow-up period: 24 weeks.
Setting: 19 centers in the United States.
Patients: 140 patients (mean age 32 y, 90% women) who met 4 classification criteria of the American College of Rheumatology for systemic lupus erythematosus; had lupus nephritis confirmed by renal biopsy and classified (World Health Organization criteria) as proliferative glomerulonephritis class III (focal), IV (diffuse), or V (membranous); and had clinical activity (i.e., ≥ 1 of the following: incident decrease in renal function [serum creatinine > 1.0 mg/dL {> 88 µmol/L}]; proteinuria [> 500 mg protein in 24-h urine specimen]; microscopic hematuria [> 5 red blood cells per high-power field]; or presence of cellular casts, increasing proteinuria with rising serum creatinine levels, active urine sediment, or serologic abnormality). Exclusion criteria included creatinine clearance < 30 mL/min, serum creatinine on repeated testing > 3.0 mg/dL (265 µmol/L), severe comorbid conditions, treatment with cyclophosphamide in past 12 months or ever with MMF, monoclonal antibody therapy in the past 30 days, and pregnancy or lactation.
Intervention: Oral MMF plus corticosteroids (n = 71) or IVC plus corticosteroids (n = 69). MMF was begun at 500 mg twice daily, increased at week 2 to 750 mg twice daily, and advanced weekly to 1000 mg 3 times/d. IVC was given as monthly pulses according to a National Institutes of Health protocol. Prednisone, 1 mg/kg of body weight, was given daily with tapering by 10% to 20% at 1- or 2-week intervals when clinical improvement was seen.
Outcomes: Complete remission at 24 weeks (i.e., return to within 10% of normal values of serum creatinine, proteinuria, and urine sediment) and adverse events.
Patient follow-up: 84% (intention-to-treat analysis).

MAIN RESULTS

More patients in the MMF group than in the IVC group had complete remission at 24 weeks (Table). The results show that MMF is both noninferior (criterion for noninferiority: lower CI limit > −10%) and superior to IVC. 3 patients in the IVC group died; the MMF group had fewer severe infections (1 vs 6 patients) and hospitalizations (0 vs 5 patients) but more diarrhea (15 vs 2 patients) than the IVC group.

CONCLUSION

In patients with active lupus nephritis, oral mycophenolate induced complete remission in more patients than did intravenous cyclophosphamide when given in addition to corticosteroids.

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*See Glossary.
†Information provided by author.

Oral mycophenolate mofetil (MMF) vs intravenous cyclophosphamide in addition to corticosteroids for active lupus nephritis at 24 weeks‡

Outcome	MMF	Cyclophosphamide	RBI (95% CI)	NNT (CI)
Complete remission	25%	7.4%	238% (28 to 825)	6 (4 to 24)

‡Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

COMMENTARY

The study by Ginzler and colleagues extends the existing literature on use of MMF for lupus nephritis. While 3 previously published randomized controlled trials have compared MMF with monthly IVC (1-3), this is the first in a North American population and helps to address previous concerns that the other studies, done in Asia, may not be generalizable to North American patients. The results suggest that MMF is noninferior to IVC for inducing remission in lupus nephritis, while resulting in fewer severe infections and a lower incidence of amenorrhea, as noted in other studies (1-3).

Although this study shows that MMF is superior to IVC for inducing remission, this finding must be interpreted with caution. Although it was a large trial relative to others done in lupus nephritis, the differences between groups are still based on a small number of patients. There was a large differential loss to follow-up, and patients assigned to IVC had lower remission rates at 24 months than other studies have reported (1, 3). In addition, blinding was not done because it was impractical, so patient knowledge of treatment assignment may overestimate the treatment effect. Furthermore, 20% of patients had class V lupus nephritis, which may respond differently to the treatments. If so, the variations in observed remission rates may not translate into improved long-term outcomes.

While this study provides further evidence that MMF may be at least similar to IVC for inducing remission in patients with diverse ethnic backgrounds without severe renal failure, questions still exist about the efficacy of MMF compared with cyclophosphamide on long-term clinical outcomes, including rates of lupus nephritis flares, progression to kidney failure, and ultimately survival. However, this study adds to a growing body of literature supporting the use of less toxic therapies in patients with lupus nephritis.

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References

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