CORRESPONDENCE

Mycophenolate Mofetil or Intravenous Cyclophosphamide in Lupus Nephritis

TO THE EDITOR: There are several reasons to be circumspect with regard to applying more widely the findings of the report by Ginzler et al. that compared cyclophosphamide and mycophenolate mofetil for the treatment of lupus nephritis (Nov. 25 issue).[1] First, about 20 percent of the subjects had membranous nephropathy, a form of lupus nephritis for which the optimal treatment remains uncertain and for which treatment with cyclophosphamide has not been rigorously studied. Second, the rather narrow group of patients with adequately preserved renal function poses an obstacle to generalizing the study results to patients with lupus who have higher burdens of renal injury and are at increased risk for renal failure[2] and may be more likely to benefit from intravenous cyclophosphamide. Third, activity and chronicity indexes are not provided for use in assessing patients' baseline risk of an unfavorable renal outcome.[2] Fourth, the rate of either complete or partial remission of nephritis in the cyclophosphamide group was lower than would normally be expected.[3,4] Finally, since renal response to intermittent intravenous cyclophosphamide appears to be delayed,[5] this effect may well have been missed because of the truncated follow-up and early-crossover design of the study.

Fotini B. Karassa, M.D.

Medical School of Thessaly University
41222 Larisa, Greece

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2. Austin HA III, Boumpas DT, Vaughan EM, Balow JE. Predicting renal outcomes in severe lupus nephritis: contributions of clinical and histologic data. Kidney Int 1994;45:544-50.
3. Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med 2004;350:971-80.
4. Contreras G, Lenz O, Roth D. Sequential therapies for proliferative lupus nephritis. N Engl J Med 2004;350:2519-20.
5. Ioannidis JP, Boki KA, Katsorida ME, et al. Remission, relapse, and re-remission of proliferative lupus nephritis treated with cyclophosphamide. Kidney Int 2000;57:258-64.

TO THE EDITOR: In the study by Ginzler et al., there appeared to be a lower rate of response to cyclophosphamide than is seen in the unit at Prince of Wales Hospital or reported in other trials.[1,2] Given that the trial by Ginzler et al. set out to demonstrate noninferiority, how is this lower-than-expected rate of response to cyclophosphamide explained by the authors? Furthermore, the patients recruited to participate in the trial appeared not to have flares of their lupus. An additional trial focusing on patients with lupus flares would be of great interest.

John Paul Killen, M.B., B.S.

Prince of Wales Hospital
Randiwick NSW 2031, Australia
ojpo@hotmail.com

1. Hu W, Liu Z, Chen H, et al. Mycophenolate mofetil vs cyclophosphamide therapy for patients with diffuse proliferative lupus nephritis. Chin Med J (Engl) 2002;115:705-9.
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pressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum 2002;46:2121-31.

THE AUTHORS REPLY: With regard to the comments of Dr. Karassa: we agree that additional data are needed before one can consider adopting mycophenolate mofetil as a single standard of care in the treatment of lupus nephritis. Indeed, a large international two-phase clinical trial involving induction and maintenance therapy with mycophenolate mofetil is currently being conducted by Aspreva Pharmaceuticals. Nevertheless, we believe that the results of our study are robust and that the inclusion of patients with pure membranous lupus nephropathy was justified. Several anecdotal series showed that the prognosis in patients with this type of lupus nephropathy was improved by the use of immunosuppressive agents in conjunction with steroids.[1,2] Furthermore, considering only the patients who had evidence of proliferative features on renal biopsy, 15 of 57 subjects randomly assigned to receive mycophenolate mofetil (26.3 percent) had a complete remission, as compared with 3 of 56 of those receiving intravenous cyclophosphamide (5.4 percent, P=0.002). Complete or partial remission occurred in 30 of 57 subjects treated with mycophenolate mofetil (52.6 percent), as compared with 17 of 56 who received intravenous cyclophosphamide (30.4 percent, P=0.03). We excluded patients with a very low probability of reversal of renal insufficiency; however, the inclusion of those with a serum creatinine level as high as 3.0 mg per deciliter or a creatinine clearance rate as low as 30 ml per minute provided the opportunity to compare the two regimens among patients with a substantial range of renal function.

We acknowledge that calculated activity and chronicity indexes on renal biopsy were not obtained, since biopsies were performed at multiple sites before study entry. Nevertheless, qualitative descriptions of activity and chronicity were reviewed. In response to Dr. Killen's concern: we made it clear that all patients in the study had active nephritis according to clinical criteria.

The noninferiority design of our trial did not influence overall response rates. The inclusion of a large proportion (56 percent) of black patients, who traditionally have a poorer prognosis for response to therapy, is likely to explain the lower-than-expected response rate in our study.

Finally, in our original discussion, we commented that the crossover design may have prevented the detection of a later time to response to intravenous cyclophosphamide. We believe that earlier response times should be considered in evaluating the efficacy of a regimen, in accord with the finding in the Euro-Lupus Nephritis Trial of the predictive value of an early response to immunosuppressive therapy with respect to subsequent good renal outcome.[3]

Ellen M. Ginzler, M.D., M.P.H.
State University of New York Downstate Medical Center
Brooklyn, NY 11203
ellen.ginzler@downstate.edu

Mary Anne Dooley, M.D., M.P.H.
University of North Carolina–Chapel Hill
Chapel Hill, NC 27599

Mimi Y. Kim, Sc.D.
Albert Einstein College of Medicine
Bronx, NY 10461

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3. Houssiau FA, Visconcelas C, D'Cruz D, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. Arthritis Rheum 2004;50:3934-40.

Digital and Film Mammography

TO THE EDITOR: Pisano et al. (Oct. 27 issue)[1] report that digital mammography is more accurate in women under the age of 50 years, women with radiographically dense breast tissue, and premenopausal or perimenopausal women. They showed that digital and film mammography are similar with respect to the overall diagnostic accuracy. The latter finding is consistent with previous reports.[2-4] We are disturbed that the authors did not provide a stratified analysis for the remainder of women, who make up more than half the study population (women 50 years of age or older, women with nondense breast tissue, and postmenopausal women).