Role of Mycophenolate Mofetil in the Treatment of Lupus Nephritis

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In patients with systemic lupus erythematosus (SLE), lupus, nephritis is present in approximately 25% of patients at the time of diagnosis and eventually develops in up to 60% of adults and 80% of children (1). Selected observational studies have reported that patients with proliferative glomerulonephritis (class III, IV, and V with intracapillary proliferation) have an average absolute risk for the development of chronic kidney disease (CKD) and all-cause mortality of approximately 25 and 13%, respectively (2–5). Treatment of patients with SLE and proliferative lupus nephritis includes the use of immunosuppressive agents in combination with corticosteroids aiming to reduce the risk for the development of CKD and death.

Optimal management of proliferative lupus nephritis with immunosuppressive agents remains a challenge because of the need to balance the efficacy and safety of the therapeutic agents. In the last 30 yr of the last century, randomized clinical trials performed primarily at the National Institutes of Health demonstrated that regimens using cyclophosphamide with corticosteroids were superior to corticosteroids alone for the treatment of proliferative lupus nephritis (6–10). The incidence of CKD was significantly lower on average of 15% in patients who received long-term cyclophosphamide compared with 45% in patients who received corticosteroids alone. Two published meta-analyses indicated that regimens of cyclophosphamide were more efficacious than regimens of corticosteroids alone, reducing the risk for the development of CKD (11,12) and all-cause mortality (11). However, the success of cyclophosphamide regimens comes with the burden of adverse events. The incidence of amenorrhea is significantly increased, ranging from 45 to 71% in patients who receive cyclophosphamide for >6 mo. In addition, the incidence of herpes zoster infection is significantly increased, ranging from 25 to 33% with the use of cyclophosphamide. Hemorrhagic cystitis is seen primarily with the long-term use of oral cyclophosphamide with an incidence ranging from 14 to 17% (6–10). The safety concerns of cyclophosphamide regimens has led to the use of azathioprine (a nonselective inhibitor of purine synthesis) with corticosteroids, which reduces the risk for all-cause mortality (12). However, azathioprine does not have a clear beneficial effect on the risk for important renal events (12,13) unless it is used after an induction regimen of cyclophosphamide (14,15).

In the past decade, the immunosuppressive agent mycophenolate mofetil (MMF) has been used in the treatment of lupus nephritis. The development of MMF, which is an ester prodrug of mycophenolic acid (MPA) with superior bioavailability (16), was based on the observations that patients with adenosine deaminase deficiency, a deficiency of the *de novo* pathway for purine synthesis, have a combined B and T cell immunodeficiency, whereas patients with hypoxanthine-guanine-phosphoribosyl transferase deficiency, a defect of the salvage pathway for purine synthesis, develop neurologic abnormalities and gout yet have essentially normal immune functions (17,18). Lymphocytes use preferentially the *de novo* pathway for synthesis of guanosine monophosphate. Therefore, inhibition of the *de novo* purine synthesis seemed to be an attractive option to modulate immune responses while limiting adverse effects of nonselective immunosuppressive agents. MPA, a fermentation product of *Penicillium brevicompactum* and related fungi, is an inhibitor of inosine monophosphate dehydrogenase, a key enzyme in the *de novo* pathway of purine synthesis. As expected, MPA *in vitro* and *in vivo* inhibits lymphocytes proliferation, modulates apoptosis in activated T lymphocytes, and attenuates the autoantibody production by B cells and the production of oxygen radicals and adhesion molecules, all essential mechanisms that propagate the autoimmune and inflammatory responses in SLE (19–21). The efficacy of MMF was demonstrated in rodent models of lupus nephritis (22,23).

The biologic plausibility for the use of MMF in the treatment of proliferative lupus nephritis has lead to the study of this agent in five induction trials, aiming to achieve remission, and one maintenance trial, aiming to prevent relapse conducive to CKD.

In one randomized, controlled trial conducted by Chan *et al.* (24), an induction regimen of MMF with corticosteroids for 12 mo ($n = 21$) was compared to an induction regimen of oral cyclophosphamide for 6 mo followed by azathioprine for 6 mo with corticosteroids ($n = 21$). The study included primarily Asian patients with diffuse proliferative glomerulonephritis. In that study, similar remission rates were reported for both groups (combined partial and complete remission rates of 95 and 90% in the MMF and sequential groups, respectively). Recently, Chan *et al.* (25) published their 5-yr follow-up data of their clinical trial in which additional patients were randomly

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assigned to receive MMF ($n = 33$) and sequential cyclophosphamide followed by azathioprine ($n = 31$). Both short- and long-term efficacies in renal outcomes were again statistically similar with the incidences of leucopenia (0 *versus* 26%; $P = 0.002$), infections (13 *versus* 40%; $P = 0.013$), and amenorrhea (4 *versus* 36%; $P = 0.004$) significantly lower in the MMF group compared to the sequential group. Although the studies of Chan *et al.* were not powered to detect a difference in hard clinical outcomes between the two arms, the encouraging results in other outcomes were mirrored in another Chinese nonrandomized, controlled trial by Hu *et al.* (26), who compared induction MMF with corticosteroids to pulses of intravenous cyclophosphamide with corticosteroids. In another randomized, controlled trial from Malaysia published by Ong *et al.* (27), an induction regimen of MMF with corticosteroids ($n = 19$) was compared to monthly pulses of intravenous cyclophosphamide with corticosteroids ($n = 25$) for 6 mo in patients with proliferative lupus nephritis. In that study, the induction regimen of MMF with corticosteroids was as effective as intravenous cyclophosphamide with corticosteroids (combined partial and complete remission rates of 58 and 52%, respectively) without difference between the two groups in the rate of adverse events. Recently, Ginzler *et al.* (28) reported that 6 mo of MMF with corticosteroids ($n = 71$) was superior to monthly pulses of intravenous cyclophosphamide with corticosteroids ($n = 69$) for 6 mo inducing complete (22.5 *versus* 5.8%; $P < 0.05$) and combined partial and complete (52.1 *versus* 30.4; $P < 0.05$) remissions of proliferative lupus nephritis in patients with SLE. The induction with MMF compared to intravenous cyclophosphamide had a more favorable safety profile with particularly fewer pyogenic infections (relative risk 0.36; $P = 0.030$). The study by Ginzler *et al.* (28) included a large proportion of African-American patients (56%), who traditionally have been thought to have a more aggressive disease course with poor response to cyclophosphamide, giving additional credence to the notion that induction therapy with MMF is an alternative to cyclophosphamide. In a recent randomized controlled trial reported by Flores-Suarez *et al.* (29), published only in abstract form, an induction regimen of MMF ($n = 10$) had similar efficacy and safety compared to intravenous cyclophosphamide ($n = 10$).

In this issue of *CJASN*, Walsh *et al.* (30) report the results of a meta-analysis that pooled four randomized, controlled trials that compared MMF to cyclophosphamide as induction agents. The relative risk for failure to induce combined partial and complete remission was 30% lower ($P = 0.004$) for patients who were treated with MMF compared to those who were treated with cyclophosphamide. At the end of the prespecified studies' duration, the relative risk for the composite outcome of ESRD or death was 65% lower for patients who were treated with MMF compared to those who were treated with cyclophosphamide; however, the 95% confidence interval (CI) of this estimate was wide and nonsignificant with a risk reduction to risk increase ranging from −90 to +22% ($P = 0.10$). Analysis of this composite outcome using the extended-study follow-up showed a significant risk reduction of 54% ($P = 0.02$) for patients who were treated with MMF compared to those who were treated with cyclophosphamide. The relative risk for infections was 36% lower for patients who were treated with MMF compared to those who were treated with cyclophosphamide; however, the 95% CI of this estimate was wide and nonsignificant, ranging from −61 to +6% ($P = 0.085$). Other adverse events were too few, resulting in inadequate power to compare both induction agents.

Another meta-analysis that evaluated MMF in lupus nephritis, pooling five induction trials, also showed that MMF was superior to cyclophosphamide (31). Combined partial and complete remission was significantly more frequent with MMF (66%) than with cyclophosphamide (54%), with a number needed to treat of eight (95% CI 4.3 to 69) to induce one additional combined partial and complete remission. Serious infections occurred less frequently with MMF (3.9%) than with cyclophosphamide (15%), with a number needed to treat of 8.7 (95% CI 5.5 to 21) to prevent one serious infectious event. Leucopenia also occurred less frequently with MMF (1.6%) than with cyclophosphamide (25%), with a number needed to treat of 4.3 (95% CI 2.9 to 8.3) to prevent one leucopenia event. Amenorrhea occurred less frequently with MMF (1.9%) than with cyclophosphamide (12%), with a number needed to treat of 9.5 (95% CI 6.2 to 20) to prevent one amenorrhea event. Diarrhea occurred more frequently with MMF (16%) than with cyclophosphamide (4%), with a number needed to treat of 8.5 (95% CI 5.3 to 21) to cause one additional diarrhea episode.

The meta-analysis by Walsh *et al.* (30) achieves its goals of pooling together four induction trials that were in most instances underpowered to detect superiority differences in outcomes of patients who were treated with MMF compared to cyclophosphamide. The consistent directionality across all studies of the superiority of MMF is reassuring. However, a meta-analysis is limited to what was studied and published in the combined studies. In most instances, the included studies were of limited quality by Jadad scores. The participants in the studies also varied with their risk for remission as shown by their varying rates of remission. With only four studies, a meta-regression exploring factors for why these studies differ cannot be done. Epidemiologic evidence suggests the importance of patient baseline characteristics (4,32), which may be associated with response to regimens such as MMF or cyclophosphamide. A patient-level meta-analysis to examine directly, for example, factors such as treatment allocation–race interaction and baseline activity of the disease, combining the actual data sets, might have helped to provide more information. The investigators mentioned other limitations worth highlighting. The participants included in those trials had a relatively preserved filtration function, and their results cannot be generalized to patients with moderately to severely reduced filtration function and rapidly progressive glomerulonephritis. Another limitation is that the result of the analysis for the composite outcome of ESRD or death using the extended-study follow-up may be related to factors other than the comparison of MMF to cyclophosphamide as induction agents. Such factors may be the actual maintenance regimen used (crossover or another immunosuppressive agent, such as azathioprine), the adherence to treatment, and the way patients were lost to

follow-up. The analysis of the extended follow-up should be considered only an observational phase, limiting the value of the treatments' comparison.

In summary, in patients with SLE, the development of proliferative lupus nephritis adds significant morbidity and mortality. The treatment options for proliferative lupus nephritis continue to evolve. In the past decade, clinical trails have defined better the role of MMF in the treatment of this disease. As highlighted by the clinical trials and the meta-analyses, MMF can be used as an induction agent for patients with active proliferative lupus nephritis and fairly preserved renal filtration function. The limitations of small, underpowered clinical trials and any meta-analysis may be helped by the ongoing large, multicenter, clinical trials that are comparing MMF as a prolonged induction/maintenance agent to cyclophosphamide or azathioprine, respectively (33,34).

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See the related article, "Mycophenolate Mofetil for Induction Therapy of Lupus Nephritis: A Systematic Review and Meta-Analysis," on pages 968–975.