

Pharmacological Therapy of Lupus Nephritis

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CASE PRESENTATION

Mrs P, a 31-year-old woman, developed a blood pressure of 170/104 mm Hg at 38 weeks of pregnancy. Her obstetrician performed a laboratory evaluation that revealed proteinuria (2+), thrombocytopenia (platelet count, $121 \times 10^3/\mu\text{L}$ [normal range: $150\text{--}350 \times 10^3/\mu\text{L}$]), a serum creatinine level of 0.8 mg/dL (70.7 $\mu\text{mol/L}$) (normal range: 0.4–1.1 mg/dL [35.3–97.2 $\mu\text{mol/L}$]), uric acid level of 9.0 mg/dL (normal range: 2.4–5.7 mg/dL), and aspartate and alanine aminotransferase levels of 170 U/L and 190 U/L, respectively (normal range: 0–35 U/L). Mrs P was diagnosed with the HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome¹ and underwent an emergent cesarean delivery of a healthy male newborn. Despite this intervention, Mrs P continued to have thrombocytopenia and hypertension. In addition, she developed temperatures up to 102° F. She was treated empirically with antibiotics and received heparin briefly for a presumptive diagnosis of pelvic thrombophlebitis. Fevers continued and she developed weakness and fatigue.

Four months after delivery, she developed progressive dyspnea on exertion and orthopnea. Echocardiography revealed an ejection fraction of 30%. Therapy was initiated with an angiotensin-converting enzyme inhibitor and a loop diuretic, with resolution of her symptoms and normalization of her cardiac function over the subse-

quent 2 months. Her transient congestive heart failure was attributed to postpartum cardiomyopathy. Five months after delivery, she presented with fever, fatigue, arthralgias, malar rash, a papular eruption on her forearms, and alopecia. Her platelet count was still low ($69 \times 10^3/\mu\text{L}$) and she remained anemic (hematocrit, 26% [normal range: 38%–47%]). These findings prompted a serological workup that revealed high titer positive assay for antinuclear antibodies (ANAs) and antibodies to double-stranded DNA (dsDNA). Her serum complement levels were low, with the C3 and C4 complements measuring 43 mg/dL (normal range: 79–152 mg/dL) and 5 mg/dL (normal range: 12–42 mg/dL), respectively. Her erythrocyte sedimentation rate was elevated at 107 mm/h (normal range: 4–25 mm/h). The diagnosis of systemic lupus erythematosus (SLE) was made.

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At the time of Mrs P's nephrology evaluation, her medications included candesartan (32 mg/d) and metoprolol succinate (150 mg/d). The family medical history was noncontributory. She had previously worked as a neonatal nurse and did not smoke or drink. Her child was now 6 months old; she and her husband were eager to have more children.

On physical examination the patient was afebrile with a blood pressure of 132/80 mm Hg, a resting pulse

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of 80/min, and a respiratory rate of 12/min. She had thinning hair and a malar rash, but her skin was otherwise clear. Her cardiac examination revealed a regular rate and rhythm, normal S_1 and S_2 , and no murmurs. Her lungs were clear to auscultation. There was no organomegaly, and she had no clubbing, cyanosis, edema, or arthritis in her extremities. The neurological examination was normal. Additional laboratory results were notable for a serum creatinine level of 1.1 mg/dL (97.2 $\mu\text{mol/L}$) with a urine protein to creatinine ratio of 2.5 mg protein/mg creatinine (proteinuria approximately 2.5 g/d). Microscopic examination of her urine showed 10 to 15 red blood cells/high power field, but no red cell casts. Further serological workup revealed antibodies to Ro and Sm.

A kidney biopsy was performed to determine the histological nature and severity of her renal process. However, given that her platelet count remained low, biopsy was delayed until after a methylprednisolone pulse, 1 g/d for 3 days, followed by 60 mg/d of prednisone. The methylprednisolone led to a platelet count increase to greater than $100 \times 10^3/\mu\text{L}$ within 5 days, and the kidney biopsy was undertaken without com-

plications. Most of the 22 glomeruli in the sample showed diffuse mesangial expansion and proliferative changes, with mesangial and endocapillary proliferation. There were segmental necrotizing lesions in 4 of the glomeruli and fibrocellular crescents in 2, indicating significant activity (representative glomeruli shown in FIGURE 1). In addition, immunofluorescence revealed a "full house" of immunoreactants, with granular staining for IgG, IgA, C3, C1q, and κ and λ light chains. The biopsy was consistent with diffuse proliferative (World Health Organization [WHO] class IV) glomerulonephritis.

A meeting including the patient, her husband, the rheumatologist, and the nephrologists was convened to discuss treatment options. Although cyclophosphamide was considered the standard of care in this setting, the patient and her husband were concerned about the potential effects of that medication on fertility, the risk of malignancy, and the possible infectious consequences of severe immunosuppression. In light of these concerns, treatment with mycophenolate mofetil was considered. Presented with a balanced discussion of the data now available on the use of mycophenolate

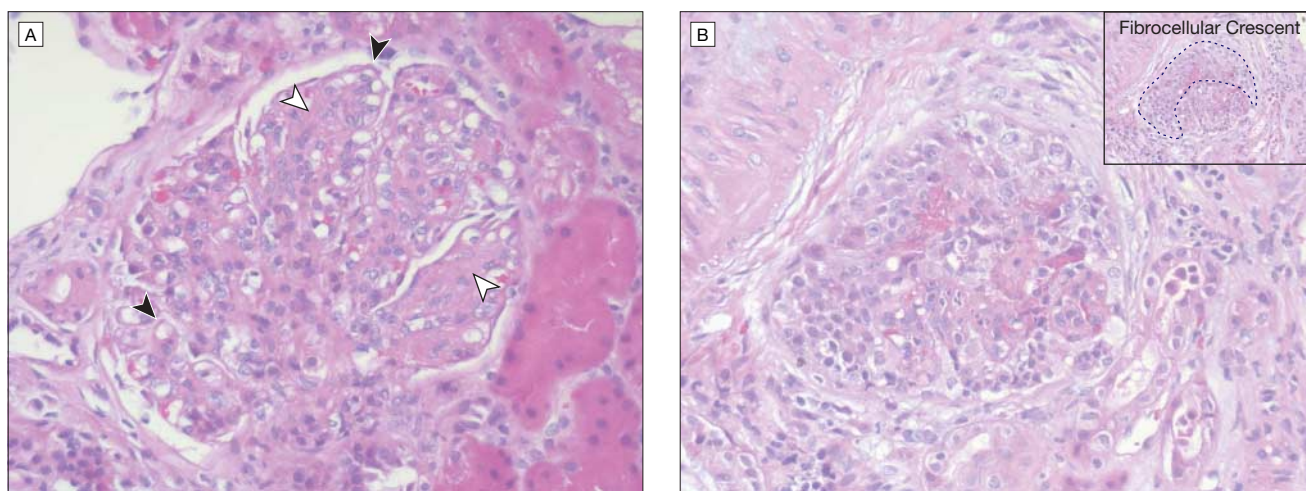
mofetil in lupus nephritis, Mrs P chose to undergo therapy with mycophenolate mofetil.

DISCUSSION

Mrs P's presentation is instructive because it highlights the fact that SLE can develop during or after pregnancy and that it can mimic preeclampsia and the HELLP syndrome. Her case also demonstrates how to approach difficult therapeutic issues by involving the patient in the decision-making process. In Mrs P's case, the particular concern related to the potential for both short- and long-term adverse effects of cyclophosphamide, particularly those related to fertility. The choice was between a standard medication associated with substantial risks of toxicity and a newer agent with a limited track record. Her case illustrates emerging data that strongly support mycophenolate mofetil as an alternative to cyclophosphamide in the treatment of lupus nephritis.

The diagnosis of SLE was suspected in this patient when she developed a malar rash, alopecia, arthralgias, and worsening fatigue, accompanied by thrombocytopenia and hemolytic anemia. The diagnosis was confirmed by positive assays for ANAs, antibodies to

Figure 1. Light Microscopic Findings of Representative Glomeruli



A, Hyperlobulated glomerulus with global involvement with endocapillary and mesangial hypercellularity with matrix expansion (white arrowheads) and wireloop lesions (black arrowheads). B, Glomerulus with global endocapillary proliferation, leukocyte influx, mesangial expansion, and crescent formation (hematoxylin-eosin stain; original magnification $\times 400$).

double-stranded DNA (dsDNA), and the findings of her renal biopsy. Her presentation was confusing because both preeclampsia and the HELLP syndrome can mimic SLE closely, and her stage of pregnancy corresponded precisely to the time at which these entities occur. The persistence of her clinical and laboratory abnormalities for months during the postpartum period were consistent with SLE as the sole cause of her presentation during pregnancy. In the absence of postpartum complications, for example, the platelet counts in the HELLP syndrome normally rebound toward normal within 1 week of delivery.¹ The confusion in the postpartum period was compounded further by her development of cardiomyopathy. Although postpartum cardiomyopathy is certainly a possible explanation, her cardiac dysfunction may also have been related to her SLE.^{2,3} Moreover, SLE-related cardiomyopathy has also been reported in the postpartum period.⁴ Systemic lupus erythematosus cardiomyopathy, like postpartum cardiomyopathy, may be associated with a waxing and waning course and spontaneous resolution.

Kidney Involvement in SLE

The kidney is a major target organ of SLE. Up to 60% of patients with SLE will develop renal manifestations at some point in their course, with 25% to 50% presenting with kidney involvement early.⁵ The clinical presentation of kidney involvement is highly variable, ranging from mild asymptomatic proteinuria to rapidly progressive glomerulonephritis. Features generally include varying degrees of glomerular involvement with proteinuria—nephrotic in 45% to 65% of cases⁵—as well as hematuria with red cell casts and/or acute renal failure.

The histopathologic manifestations of lupus nephritis are classified into several categories designated by the WHO classification. These criteria have undergone several revisions, the most recent of which evolved under the auspices of both the International Society

Table 1. Classification and Treatment of the Different Forms of Lupus Nephritis

WHO Class*	Description	Immunosuppression Recommendations†
I	Minimal mesangial lupus nephritis	No specific therapy
II	Mesangial proliferative lupus nephritis	No specific therapy
III	Focal (proliferative) lupus nephritis	Mild: none or glucocorticoids Severe: see treatment for class IV below
IV	Diffuse (proliferative) lupus nephritis	Induction (6 mo): cyclophosphamide or mycophenolate mofetil Maintenance: mycophenolate mofetil or azathioprine
V	Membranous lupus nephritis	Glucocorticoid with or without cyclosporine
VI	Advanced sclerosing lupus nephritis	No specific therapy

Abbreviation: WHO, World Health Organization.
*Subclasses omitted (see Weening et al⁶ for full classification).
†Recommendations derived from Rose et al.⁷

of Nephrology and the Renal Pathology Society.⁶ The general structure includes 6 principal pathological patterns (classes I-VI) (TABLE 1).

The focal and diffuse proliferative forms of lupus nephritis (classes III and IV, respectively) are distinguished from each other only by the percentage of glomeruli involved. These renal lesions generally present with microscopic hematuria with or without red blood cell casts, varying degrees of proteinuria, and progressive renal failure. In contrast, the membranous lesion (class V) typically presents with nephrotic-range proteinuria. Several studies, however, have illustrated the unreliability of diagnoses rendered on the basis of clinical features alone.⁸⁻¹⁰ Because the optimal treatment varies with the type of glomerular disease, kidney biopsy should be performed to make a definitive diagnosis.^{11,12} In addition to histopathologic confirmation of the WHO class, biopsy provides important prognostic information by permitting the pathologist to assess both activity and chronicity.^{13,14}

Histological activity and chronicity scores have been developed to allow for improved prediction of the progression of lupus nephritis.¹⁵ Of the features indicating activity, the presence of cellular crescents^{13,15,16} and fibrinoid necrosis¹⁵ appear to have the highest predictive value for poorer outcome. When using the chronicity index, which includes features such as glomerular sclerosis and interstitial fibrosis, a higher

score is associated with a worse prognosis.^{15,17,18} The absence of chronic changes is particularly informative as these patients have an excellent prognosis.¹⁹ Therefore, when chronicity is limited, therapeutic interventions are likely to have maximum benefit.

In Mrs P's case, the presence of an elevation of her creatinine level with hematuria and moderate levels of proteinuria suggested most likely the presence of a class III or IV proliferative lesion, although without biopsy these could not be distinguished. Particularly important was the need to determine the severity of the activity, as the clinical presentation associated with mild histopathologic activity can be very similar to one seen with more active histopathology earlier in its development. Indeed, in this case, despite relatively mild clinical features, significant disease activity was present.

The differential diagnosis of kidney involvement in SLE extends beyond the WHO classification to include renal thrombotic microangiopathy, usually related to presence of antiphospholipid antibodies, which may be present in 15% to 90% of SLE patients.²⁰ Other nonlupus causes of kidney disease that may affect a person of similar age or sex (eg, IgA nephropathy, thin basement membrane disease) must also be considered. The differentiation of these disorders is once again enhanced by performance of a kidney biopsy.

Current Treatment Options in Lupus Nephritis

The optimal treatment regimen⁷ in lupus nephritis varies according to WHO class^{3,14} (Table 1). Patients with the mildest forms of lupus nephritis (WHO class I or II) generally do well without specific intervention. In the absence of appropriate immunosuppressive therapy, however, the proliferative forms (class III and IV) of lupus nephritis typically progress to chronic renal failure.²¹ The benefits of early treatment are well documented.²² This has led to a propensity to treat all patients with proliferative lesions regardless of severity. In patients such as Mrs P, who have the most severe forms of lupus nephritis, aggressive immunosuppressive therapy is warranted.

Cyclophosphamide in the Treatment of Lupus Nephritis

Early treatment regimens for class IV lupus nephritis involved predominantly the use of high-dose glucocorticoids. Remissions on low doses were difficult to maintain, and most patients required high doses of glucocorticoids for long periods of time to achieve control of the disease. Due to the significant toxicity and poor long-term outcome, the search for more effective and glucocorticoid-sparing regimens began. In early trials, cyclophosphamide in combination with glucocorticoids demonstrated improved renal survival over glucocorticoid therapy alone²³ and achieved lower rates of recurrence.²⁴ Intravenous cyclophosphamide became preferred over the oral agent due to perceived lower levels of toxicity. Subsequent studies showed that longer duration of therapy during the maintenance phase improved remission rates.²⁵

Based on investigations conducted at the National Institutes of Health (NIH) over the past 20 years,^{23,25-27} intravenous cyclophosphamide became the standard therapy for class IV lupus nephritis.²⁸ Had Mrs P undergone therapy with this agent, she would have received cyclophosphamide in an intravenous form as a bolus in combina-

tion with glucocorticoid therapy. Following the protocol popularized by the NIH investigators, intravenous cyclophosphamide is used as induction therapy, administered monthly at a dose of 0.5 to 1 g/m² of body surface area for 6 months. During the maintenance phase, cyclophosphamide is administered at the same dose as induction therapy for 4 to 6 additional cycles. Intravenous methylprednisolone treatment (1 g/d for 3 days) is frequently administered at initiation of therapy, followed by tapering oral doses starting at 0.5 to 1.0 mg/kg/d. Based on studies that have evaluated the efficacy of intermittent glucocorticoid pulses, many patients also receive monthly methylprednisolone pulses on the same day they receive cyclophosphamide.^{27,29}

Cyclophosphamide Toxicity

Mrs P's concerns about the potential toxicities of cyclophosphamide and her desire to avoid the drug were well founded. Immediate toxicity of pulse cyclophosphamide includes nausea, vomiting, hair loss, and fatigue. Major toxicities include cytopenias, serious infections, hemorrhagic cystitis, malignancy, and, of great importance to this patient, gonadal failure.³⁰ Serious infections are common in SLE, and death from infection correlates with the recent use of glucocorticoids and cyclophosphamide.^{30,31}

Although their renal outcomes were significantly improved and they had reduced glucocorticoid exposure, patients treated with cyclophosphamide under NIH protocol had more adverse effects in both short- and long-term follow-up when compared with glucocorticoids alone.^{27,29} Mortality was 7.4%²⁷ with initial cyclophosphamide administration (mean follow-up, 5 years) and 19% at a median 11 years of follow-up,²⁹ compared with 0% and 4%, respectively, in the glucocorticoid treatment arm. These high mortality rates with the use of cyclophosphamide, insufficiently acknowledged in some reviews, must be considered when contemplating the use of cyclophosphamide. It must

also be recognized, however, that earlier trials of cyclophosphamide used higher doses for longer durations than the current standard regimens. Among patients treated with cyclophosphamide in one study, 26% developed infection compared with 7% in the glucocorticoid group.²⁷ However, there was no difference in infection rates on long-term follow-up, although trends consistently show higher infection rates with cyclophosphamide treatment. This is illustrated by the higher incidence of herpes zoster infection in 15% of patients (vs 4% with glucocorticoids) and cervical dysplasia in 11% of patients (vs 0% with glucocorticoids). Other notable complications during treatment include the development of avascular necrosis in 11% of patients (vs 22% with glucocorticoids alone). However, the only adverse effect to achieve statistical significance between the cyclophosphamide and glucocorticoid only groups was amenorrhea (52% vs 10%; $P < .001$).²⁷

Cyclophosphamide and Ovarian Failure

The devastating complication of gonadal failure is well described with the NIH regimen, with rates of ovarian failure ranging from 26% to 52%.^{27,32,33} The risk of toxicity increases with both dose and duration of cyclophosphamide therapy. Moreover, amenorrhea is more likely to occur in older women. Boumpas et al³³ found that 12% of those treated with 7 monthly cyclophosphamide doses developed amenorrhea, compared with 39% of those who received more than 14 doses ($P = .07$). Rates also increased with older age, with only 12% of patients 25 years or younger developing sustained amenorrhea, compared with 27% of patients 26 to 30 years old and 62% of patients older than 30 years ($P = .04$). Although young women may not develop ovarian failure at rates as high in short-term follow-up, they are likely to experience menopause earlier. In an extended follow-up of up to 11 years of an earlier NIH cohort,²⁷ 60% of those treated with cyclophosphamide developed amenorrhea.

Preservation of ovarian function by inducing gonadal quiescence with gonadotropin-releasing hormone antagonists has been recommended.^{34,35} Although no large studies have been performed, several small studies suggest that these agents have the potential to prevent ovarian failure.^{34,36-38} The largest study in SLE patients involved 36 women treated with cyclophosphamide. Chronic amenorrhea occurred in 11% of those treated with concomitant leuprolide and 39% of those without it ($P=.06$). The most serious adverse effect of leuprolide is the potential for bone mineral density loss caused by relative estrogen deficiency.³⁵ Under ideal circumstances, leuprolide is administered 3 to 4 weeks before the first dose of cyclophosphamide, but in the presence of acute, life-threatening disease, this is usually not an option. In such instances, leuprolide may be given closer to the first dose.³⁵ Other options include oocyte cryopreservation or preservation of fertilized eggs. These alternatives also suffer from the time constraints necessary for the induction of hyperovulation.

Need for Non-Cyclophosphamide-Based Regimens

Although many patients with proliferative lupus nephritis achieve remissions with the current cyclophosphamide regimens, there remain significant numbers of treatment failure and renal disease relapses. In view of the failure of cyclophosphamide-based regimens to induce lasting remissions in many patients and the substantial toxicity associated with this medication, the development of alternative approaches to treatment is essential. In a recent study³⁹ in which women were asked about hypothetical treatment preferences, 98% stated that they would choose azathioprine over cyclophosphamide if the 2 medications were considered equally effective. Even given a theoretical probability of renal survival of 100% at 5 years with cyclophosphamide, a substantial minority of 31% would still have preferred azathioprine, given the risk of ovarian failure

with cyclophosphamide.³⁹ Although alternatives to cyclophosphamide have been assessed, until the introduction of mycophenolate mofetil, none had shown the potential to rival cyclophosphamide in efficacy while surpassing it in safety.

Use of Mycophenolate Mofetil in the Treatment of Lupus Nephritis

Mycophenolate mofetil is metabolized to the active immunosuppressant mycophenolic acid. Through the inhibition of the enzyme inosine monophosphate dehydrogenase by its metabolite, mycophenolate mofetil blocks *de novo* synthesis of purines, a pathway essential for the synthesis of DNA in lymphocytes.⁴⁰ Through this mechanism, it inhibits B and T cell proliferation, antibody formation, and generation of cytotoxic T cells. In addition, mycophenolate mofetil inhibits the expression of adhesion molecules on endothelial cells⁴¹ and down-regulates mesangial cell proliferation.⁴¹

Due to its history as an immunosuppressant in solid-organ transplantation, mycophenolate mofetil generated interest as a possible therapy for lupus nephritis. The use of mycophenolate mofetil in the treatment of human glomerular disease was pioneered by Briggs and colleagues,⁴² who treated 2 patients with proliferative lupus nephritis effectively with mycophenolate mofetil. Dooley and colleagues⁴³ subsequently reported a series of 13 patients with lupus nephritis, 12 of whom had class IV disease, who did not respond to cyclophosphamide therapy. In that series, only 1 patient experienced an elevation in serum creatinine level over the course of the study; 2 patients had increasing proteinuria. Adverse effects reported included pancreatitis ($n=1$), herpes simplex stomatitis associated with severe leukopenia ($n=1$), pneumonia without leukopenia ($n=1$), asymptomatic leukopenia ($n=2$), and nausea/diarrhea ($n=2$). Based on the apparent success in this and other reports in addition to a potentially more limited adverse effect profile (TABLE 2),⁴⁴⁻⁴⁷ ran-

Table 2. Selected Adverse Reactions Reported in More Than 10% of Patients Treated With Mycophenolate Mofetil*

Adverse Reaction	Frequency in Treatment Groups, %	Frequency in Placebo Groups, %
Abdominal pain	12-28	11
Diarrhea	16-36	14
Vomiting	13-14	...
Infection†	18-21	14
Urinary tract infection	37-46	...
Leukopenia	12-35	4
Anemia	25	...

*Ellipses indicates comparative placebo data not reported.
†Most common in transplant patients receiving combination immunosuppression (includes cytomegalovirus, herpes zoster, and mucocutaneous fungal infections).⁴⁴⁻⁴⁷

domized trials began. Two trials that assessed the role of mycophenolate mofetil in remission induction and one that evaluated the use of mycophenolate mofetil as a remission maintenance agent are discussed below. All 3 of these investigations were randomized, but not blinded.

Mycophenolate Mofetil and Induction Therapy for Lupus Nephritis

The first randomized trial of induction therapy with mycophenolate mofetil was conducted in Hong Kong.⁴⁸ Forty-two patients with diffuse proliferative lupus nephritis (WHO class IV) were assigned to receive either mycophenolate mofetil (1 g twice a day) or oral cyclophosphamide (2.5 mg/kg/d). Patients in both treatment arms received prednisolone (starting dose 0.8 mg/kg/d tapered to 10 mg/d by 6 months). For maintenance therapy during the second 6 months of therapy, the patients treated with mycophenolate mofetil had a 50% reduction of their dose and the patients treated with cyclophosphamide were switched to azathioprine (2.5 mg/kg/d). Both groups continued taking prednisolone at low to moderate doses. Complete remission, defined as a stable serum creatinine level (<15% above baseline), normal urine sediment, and less than 0.3 g/d of proteinuria, was achieved in 81% of those treated with mycophenolate mofetil and 76% of those treated with oral cyclophosphamide ($P>.99$) (TABLE 3). The

nolate mofetil (1500 mg twice daily) higher than that used in the Hong Kong study.⁴⁸ The rationale for the higher mycophenolate mofetil dose was evidence in the transplantation literature that African Americans, who comprised 56% of the trial cohort in the US study, require higher doses of mycophenolate mofetil than whites.⁵¹ Although mycophenolate mofetil was superior to cyclophosphamide in remission induction, the preliminary data showed much lower rates of remission with induction than in the Hong Kong trial. Only 21% of those receiving mycophenolate mofetil and 6% of those receiving cyclophosphamide achieved complete remissions in the US study ($P=.005$). Some of the disparity between the 2 studies can be explained by racial differences between the cohorts (black race predicts poorer outcome in class IV lupus nephritis^{52,53}). There may also have been differences in the histological severity and clinical severity of disease in the 2 trials. Other potential explanations include the route of therapy (intravenous vs oral) and the doses of glucocorticoids used. The definitions of remission were similar and probably cannot explain the differences seen. Because detailed data from the latter trial are not available, these explanations remain speculative.

Mycophenolate Mofetil and Maintenance Therapy

Another major trial recently evaluated the use of mycophenolate mofetil in remission maintenance.⁵⁰ After induction with 4 to 7 months of 0.5 to 1 g/m² of intravenous cyclophosphamide, patients were randomized to 1 of 3 treatment groups (Table 3): quarterly intravenous cyclophosphamide, daily oral mycophenolate mofetil, or daily oral azathioprine. Although the cumulative rate of renal survival did not differ significantly between the groups, those in the cyclophosphamide group had an increased relapse rate compared with mycophenolate mofetil, increased mortality compared with azathioprine, and increased drug-related morbidity compared with both the mycophenolate

mofetil and azathioprine groups. Although these results support the use of mycophenolate mofetil (and azathioprine) in maintenance therapy, there are several major limitations.⁵⁴ First, the definition of remission—reduction in the urine protein:creatinine ratio to less than 3 if nephrotic at enrollment, and a ratio 50% of baseline if subnephrotic—was less stringent in comparison to other trials. Second, many patients did not reach a satisfactory remission by the end of the induction phase, which made it likely that they would fare poorly with the same drug (cyclophosphamide) continued in the maintenance phase. Overall, the poor response to induction seen in this study can in large part be accounted for by the large proportion of Hispanic and black patients (5% were white).⁵²

CASE RESOLUTION

Mrs P began receiving mycophenolate mofetil, 1000 mg twice daily in addition to the 60 mg daily of prednisone. Within weeks, her serum creatinine level had improved from 1.1 mg/dL (97.2 μ mol/L) to 0.8 mg/dL (70.7 μ mol/L) and her thrombocytopenia had resolved. Her hematocrit increased to 35% and her complement levels normalized. After an initially sharp increase in proteinuria, within 3 months, her proteinuria had decreased to less than 1 g/mg creatinine (FIGURE 2). Prednisone was tapered and discontinued 5 months after the initiation of mycophenolate mofetil. No longer taking prednisone for over 4 months, Mrs P has maintained improved renal function (serum creatinine level, 0.8 mg/dL [70.7 μ mol/L]) and proteinuria (0.4 g/mg creatinine), a stable hematocrit and platelet count, and normocomplementemia. Mild fatigue and a minimal malar rash remain her only current symptoms. We plan to complete 18 months of maintenance therapy, based on the experience when using cyclophosphamide. Because mycophenolate mofetil is contraindicated in pregnancy, future pregnancy could be considered after the maintenance course if she remains in remission. Other ma-

ior issues surrounding the risk of future pregnancy—the risk of an SLE flare, preeclampsia, premature delivery, or poor fetal outcome⁵⁵⁻⁵⁸—continue to be discussed with Mrs P on a regular basis.

CONCLUSION

Mycophenolate mofetil has substantial appeal as a new approach to the treatment of lupus nephritis. Additional data related to the use of mycophenolate mofetil, including long-term remission and relapse rates, ideal length of treatment, optimal glucocorticoid tapering, and long-term toxicities, are the subject of ongoing studies. For now, as Mrs P's case demonstrates, mycophenolate mofetil is a reasonable option for many patients with lupus nephritis who seek a safer, effective alternative to cyclophosphamide.

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