Mycophenolate Mofetil: A Magic Bullet for Lupus?

Mycophenolic acid, the parent drug from which mycophenolate mofetil (MMF) was synthesized, was isolated from *Penicillium* species in 1896 at about the same time that quinine was first used for the treatment of cutaneous lupus. Like quinine, widespread application of mycophenolic acid (MPA) to lupus awaited synthesis of a more effective and better tolerated derivative, but the timetable was slower. During the decades between 1920 and 1960, the quinine derivatives quinacrine, chloroquine, and hydroxychloroquine were synthesized and gained wide acceptance for treatment of lupus, particularly cutaneous lupus. Much later, in the 1960s, MPA was found to have antifungal and anticancer properties.

Mycophenolic acid was first extensively studied for treatment of psoriasis in the 1970s, employing heroic doses of 4–9 grams per day. Although MPA was shown to be an effective treatment for psoriasis, its erratic absorption, short half-life in the blood, and extremely high incidence of gastrointestinal toxicity precluded widespread use. In retrospect, unrecognized enzymes in the skin that resynthesize the active compound, MPA, from the circulating inactive metabolite mycophenolic acid glucuronide (MPAG) may have contributed to the effectiveness of MPA in psoriasis.

Introduction of MMF, which is more consistently absorbed than MPA and is hydrolyzed to MPA in vivo, enabled maintenance of therapeutic serum levels of MPA utilizing lower and better tolerated daily doses — usually 2 to 3 grams of MMF. The improved efficacy and markedly reduced toxicity of MMF led to its widespread use as an immunosuppressive. Nonetheless, individual differences in the rates of hepatic metabolism of MPA to MPAG and the renal excretion, de-glucuronidation, and reactivation of MPAG in tissues, including the intestine and skin, led to substantial variation of MPA concentrations in individual patients taking MMF. Unfortunately, determining pharmacokinetics or comparing effective drug levels in individual patients or clinical trials at this time remains cumbersome and expensive.

MMF initially “earned its spurs” by establishing itself as an effective antirejection drug in renal transplantation and was subsequently found to be effective in heart, lung, and other solid organ transplants. Two large trials comparing MMF versus azathioprine (AZA) and a third comparing MMF versus placebo in allogeneic renal transplant established its efficacy by showing a statistically significant reduction of the incidence of rejection and corticosteroid use. One successful protocol for allogeneic renal transplant utilizing MMF included no prednisone. MMF may be particularly well suited for renal transplant because decreased creatinine clearance resulting from rejection results in reduced excretion of MPAG, resulting in increased de-glucuronidation of MPAG and increased MPA levels, thereby “self-treating” the rejection episode! Renal transplant trials suggested that there was no difference in rates of rejection between regimens utilizing MMF at 2 versus 3 g per day, but that the rate of toxicity, particularly gastrointestinal toxicity, was increased in the 3 g per day groups. These results lent support to doses of about 2 g per day for transplantation and other indications, and were the basis for initial selection of 2 g per day as the target dose for lupus patients in our institution. Since then, controversy over higher dose requirements in individuals of African descent possibly due to a more rapid metabolism of MMF has arisen.

In addition to successfully preventing rejection and reducing corticosteroid use in transplantation, MMF’s known and emerging benefits may increase efficacy and decrease toxicity in the treatment of systemic lupus erythematosus (SLE) compared with currently used medications. The observation of decreased antibody levels in response to immunization in MMF versus AZA treated transplant patients suggests that auto-antibody synthesis might be sim-

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iliarily suppressed more by MMF than AZA\textsuperscript{11}. Although inhibition of antibody production may be MMF’s obvious benefit in SLE, other immunologic mechanisms such as decreased recruitment of mononuclear cells to areas of inflammation — likely via decreased expression of adhesion molecules\textsuperscript{12} — may confer benefit as well. Studies in mouse models of lupus nephritis (LN) suggest a decrease in nitric oxide production may underlie the effectiveness of MMF in LN, perhaps independent of its immunosuppressive properties\textsuperscript{13}.

Given the impact of cardiovascular disease on longterm survival of patients with lupus, it is intriguing and timely that MMF’s success in reducing transplant rejection may be based on a mechanism of reduced endothelial injury and vascular damage, again, independent of its immunosuppressive properties. In the rat aortic allograft model, MMF appeared to inhibit vascular smooth muscle cell proliferation by inhibition of endothelin-1\textsuperscript{14}. In human cardiac allograft patients, Weis and colleagues showed decreased markers of endothelial damage early in the transplant period in MMF-containing posttransplant immunosuppression regimens compared with AZA\textsuperscript{15}. As noted by Pisoni, \textit{et al}\textsuperscript{16} in this issue of \textit{The Journal}, since MMF preferentially targets activated lymphocytes, MMF may be less toxic to other bone marrow cell lines than immunosuppressive agents such as AZA. In comparison with cyclophosphamide (CYC), MMF lacks gonadal toxicity and appears to be associated with fewer secondary malignancies. Based on anecdotal experience, MMF appears less toxic than CYC during pregnancy. The overall rate of adverse events in this study as well as that from our group\textsuperscript{17} appears to be 30–40\%, but most problems were minor.

Published clinical trials have focused on the use of MMF in LN. Open trials have almost uniformly shown control of the inflammatory response and induction of remission over the short term when administered to patients who have continued active disease after taking CYC or those who have not tolerated CYC. Use of MMF as a first-line agent for active LN has been the subject of several controlled trials, some of which illustrate the complexity of applying such data to clinical practice. The study by Chan, \textit{et al}\textsuperscript{18} randomized patients with moderately active lupus to a complex regimen of daily oral CYC followed by AZA, or to initial MMF followed by AZA. The short term results\textsuperscript{18}, which suggested no difference in the MMF group compared with daily CYC, do not actually permit comparison of MMF with monthly bolus CYC. In particular, comparisons of toxicity cannot be extrapolated to monthly bolus CYC because of higher cumulative doses in patients treated with daily versus monthly bolus CYC. It is encouraging that their more recent report after a mean of 63 months continued to show no difference between the groups\textsuperscript{19}.

The recent study by Ginzler, \textit{et al}\textsuperscript{20}, which randomized patients at the time they presented with severe active LN to either MMF or monthly bolus CYC, used a higher dose of MMF, 3 g per day, than in some series, including the current study by Pisoni, \textit{et al}\textsuperscript{16}. Their report of equivalent to superior results with MMF versus monthly bolus CYC and of reduced toxicity in the MMF group after 6 months' followup should be viewed in the context of the high dose of MMF used. It is noteworthy that in this non-blinded trial, MMF at 3 g per day was well tolerated by most patients, in contrast to other series, including our own\textsuperscript{17}. It is tempting to speculate that the immediate prospect of being switched to monthly bolus CYC if MMF was not tolerated led these patients to consider frequently encountered issues such as gastrointestinal complaints to be less significant. Finally, the study by Hu, \textit{et al}\textsuperscript{21}, which reported efficacy of MMF versus monthly bolus CYC for LN in a randomized open trial, is noteworthy because of the data from serial renal biopsies that were obtained from a subset of patients. These data suggested a greater fall in disease activity indexes in the MMF versus monthly bolus CYC group and also a trend toward greater improvement of vascular lesions (“renal vasculitis or necrotizing vasculopathy”) in the MMF group (Table 1).

Chronicity indexes worsened only slightly in both groups. The reported improvement of histological signs of vascular injury is noteworthy in the context of MMF’s favorable influence on the outcome of endothelial injury in transplantation as discussed above. These results make it plausible that MMF may have at least equivalent efficacy compared with monthly bolus CYC in new LN, and that favorable short term clinical improvement may not be, as some fear, masking histological disease progression that will become clinically significant in 5–10 years. Finally, it is arguable that monthly bolus CYC plus monthly bolus methylprednisolone, which has been reported to be more effective than monthly bolus CYC alone\textsuperscript{22}, may be considered the gold standard.

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Cell infiltration & MMF Group \textsuperscript{a} & CYC Group \textsuperscript{a} & \textit{p} & \\
> 10 cells/glo & Pre-RX & Post RX & Pre-RX & Post-RX, n (%) \\
\hline
Immune complex\textsuperscript{b} & 10 (66.7) & 0\textsuperscript{**} & 9 (75) & 3 (25)\textsuperscript{**} \\
Immunocomplex deposition & 11 (73.3) & 1 (6.6)\textsuperscript{**} & 10 (83.3) & 4 (33.3)\textsuperscript{*} \\
Glomerular tuft necrosis & 11 (73.3) & 0\textsuperscript{**} & 10 (83.3) & 5 (41.7)\textsuperscript{*} \\
Microthrombi & 7 (46.7) & 0\textsuperscript{**} & 3 (25.0) & 1 (8.3) \\
Crescent\textsuperscript{c} & 11 (73.3) & 4 (33.3)\textsuperscript{*} & 7 (58.3) & 4 (33.3) \\
Renal vasculopathy\textsuperscript{c} & 10 (66.7) & 3 (20.0)\textsuperscript{*} & 5 (41.7) & 2 (16.7) \\
Activity index & 16.4 ± 7.8 & 4.0 ± 2.0\textsuperscript{**} & 12.3 ± 4.0 & 6.4 ± 3.0\textsuperscript{**} \\
Chronicity index & 1.7 ± 1.0 & 2.8 ± 2.8 & 1.5 ± 1.1 & 2.2 ± 2.3 \\
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\textsuperscript{a}Immune complex; \textsuperscript{b}cellular or fibrocellular crescent; \textsuperscript{c}included necrotizing vasculopathy and vasculitis. Post-RX vs Pre-RX in 2 groups (* \textit{p} < 0.05, ** \textit{p} < 0.01); Post-RX MMF vs CYC group (* \textit{p} < 0.05).
Although more work is required to establish MMF as the standard of care for initial treatment of LN, it is our opinion that, following monthly bolus CYC to induce remission, MMF (and possibly AZA) as maintenance therapy for LN will soon become the standard of care, at least for adults. This is supported by the study of Contreras, et al, in which maintenance therapy with MMF was found to be superior to maintenance with quarterly bolus CYC in terms of renal outcome and mortality and with overall lower toxicity. It should be noted, however, that mortality in the quarterly bolus CYC group was surprisingly high, perhaps reflecting the relatively small number of patients in each group.

No study has convincingly established superiority of MMF versus AZA for maintenance therapy of LN after monthly bolus CYC; AZA, like MMF, is much less toxic than monthly bolus CYC. For example, the recent Euro Lupus Nephritis Trial, which compared low dose to high dose intravenous CYC, used AZA as maintenance therapy and reported good results in both short and long-term follow-up. AZA currently has the advantage of being less expensive than MMF. It may reasonably be concluded that when monthly bolus CYC is employed, sequential therapy will be here to stay, especially when avoidance of gonadal toxicity is a consideration. In addition, combining sequential therapy with ovarian protection from CYC-induced damage utilizing gonadotropin-releasing hormone agonists has been proposed by our group and others.

The study by Pisoni, et al adds further support to the use of MMF in patients with both renal and non-renal SLE. The study includes “real-life” patients treated in a lupus center for a variety of disease manifestations that had not remitted despite immunosuppressive agents, including, in some cases, prior treatment with CYC. The favorable response of the majority of these patients suggests MMF can be used in refractory cases with satisfactory response and acceptable toxicity. In the absence of a control group the rate of disease improvement that might have occurred due to “regression toward the mean” or as a result of increased corticosteroid dosage is unknown, but it is clear that patients improved and that in many cases toxicity from CYC was avoided.

At this stage in our understanding of MMF for treatment of lupus we propose the following:
1. MMF levels are unpredictable, particularly in individuals with renal insufficiency; in the setting of significant renal failure, guidelines for using bolus CYC are better tested. Methods to cost effectively follow MMF levels in clinical trials need to be developed.
2. As with many lupus therapies, the benefits of MMF may be organ-specific. For example, MMF could be highly effective in the kidney and skin, but not particularly effective for synovitis. Individual patients may respond differently to different immunosuppressive regimens — one immunosuppressive will not fit all.
3. MMF 3 g per day as first-line therapy of LN has, thus far, been equivalent to bolus monthly CYC (without monthly bolus methylprednisolone) in relatively short term controlled trials. MMF is a candidate to become first-line therapy for LN on the basis of additional studies and sufficient longterm data for comparison.
4. Based on the above studies suggesting MMF is comparable to monthly bolus CYC in initial therapy of LN, the finding that MMF is equivalent or superior to quarterly bolus CYC for maintenance of remission of LN is highly plausible. The role of MMF in sequential therapy of LN needs further study, but in the absence of more data this is a reasonable strategy to use in many clinical situations.
5. MMF has not been shown to be superior as a maintenance drug to AZA after monthly bolus CYC for LN. The expense of MMF compared to AZA makes this an important consideration.

In conclusion, intriguing questions remain:
1. When used without corticosteroids, will MMF prove more effective than other immunosuppressives such as AZA, as suggested in renal transplantation? Improved ability to taper prednisone to zero during maintenance immunosuppression would be a substantial benefit.
2. What is the role of MMF for treatment of severe lupus flares during pregnancy? There are insufficient data to justify use in pregnancy, but there is no reason to believe MMF will prove more dangerous than other immunosuppressives used in renal transplantation, such as AZA or cyclosporine. The answer may come from the transplant experience.
3. Is MMF faster acting than AZA for lupus? Older trials comparing AZA with CYC suggest inferiority of AZA when used de novo for active nephritis; this might reflect slower onset of action during rapid disease progression.
4. Will MMF help protect lupus patients from vascular damage independently of its direct effects on lupus activity? This would make MMF a “triple threat”: immunosuppressive, corticosteroid and cyclophosphamide-sparing, and cardioprotective.

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