invited review

Experimental and clinical rationale for use of MMF in nontransplant progressive nephropathies

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The incidence of chronic progressive nephropathies has grown steadily in the past decades, leading to a parallel increase in both the incidence and the prevalence of end-stage renal disease (ESRD) (77). In most countries, ESRD has become an important social, medical, and financial problem, which tends to be aggravated in years to come. Several treatments intended to arrest or mitigate the progression of chronic nephropathies to ESRD have been proposed in the past few decades. These include the use of immunosuppressors (for immune-mediated nephropathies), dietary protein restriction (33, 40), and especially the use of angiotensin-converting enzyme (ACE) inhibitors (3, 44, 86) and angiotensin II receptor blockers (8, 45). Although in the long run the introduction of these compounds in medical practice will likely change the natural history of chronic renal diseases, a large fraction of treated patients still progress to ESRD (8, 44, 45), stressing the need for the development of additional therapeutic maneuvers. Mycophenolate mofetil (MMF), a compound that has been extensively used in the treatment of allograft rejection, is one of the newest promises in this regard. The fact that the same drug may serve in the treatment of transplant rejection, immune-mediated primary nephropathies, and immune-unrelated nephropathies is strongly suggestive that these processes share a number of pathogenic mechanisms, as will be pointed out later.

MMF: HISTORICAL ASPECTS

MMF is the morpholinoethyl ester of mycophenolic acid (MPA), which is released after oral administration and constitutes the actually active compound. MPA is not exactly a novel drug, having been isolated from Penicillium cultures as early as in 1896 and purified in 1913. In the 1940s, MPA was found to possess significant antibacterial and antifungal activity, although this property could not be brought to practical use. In the late 1960s, MPA was shown to inhibit cell proliferation in vitro, although it had only limited beneficial effect in cancer patients. However, MPA did have immunosuppressive proper-
ties, and evidence that it might be useful in the prevention of allograft rejection came in 1972 (60). In 1987, MPA, already used in its precursor form, MMF (initially denoted RS-61443), was shown to successfully prevent acute experimental allograft rejection (53). In the early 1990s, MMF was first used in the treatment of acute human organ rejection (75). In 1995, MMF was approved by the Federal Drug Administration for use in US renal transplant patients, becoming largely used worldwide in the years that ensued.

MECHANISM OF ACTION OF MPA

MPA arrests lymphocyte proliferation by inhibiting inosine monophosphate dehydrogenase (IMPDH), a crucial enzyme in the de novo pathway of GTP synthesis (17). In most eukaryotic cells, IMPDH inhibition has little effect on cell division because GTP can also be generated from nucleotide breakdown products. Because lymphocytes lack this “salvage pathway,” MPA specifically inhibits their proliferation, thus limiting cell-mediated immunity (17). MPA also inhibits the proliferation of vascular smooth muscle and mesangial cells (31, 66) and may therefore limit glomerular and vascular injury directly. MMF may also inhibit the proliferation of monocytes (54) and fibroblasts (4) and induce apoptosis of monocytes (12). In addition, MPA may inhibit the glycosylation and, consequently, the affinity of adhesion molecules expressed by lymphocytes and endothelial cells (6, 32, 65), again as a result of intracellular GTP depletion, thus limiting lymphocyte migration into the renal tissue. Therefore, MPA affects several crucial aspects of the inflammatory response, as will be discussed below. However, given the relative specificity of its effect, MPA has little impact on other tissues with high proliferative activity, such as skin, intestine and bone marrow. This property is what makes MMF suited to treat allograft rejection in place of more toxic immunosuppressors. Nevertheless, MPA is not entirely devoid of toxic effects, as will be noted in UNTOWARD EFFECTS OF MMF THERAPY.

USE OF MMF IN NONTRANSPLANT IMMUNE-MEDIATED NEPHROPATHIES

Pathogenesis of Immune-Mediated Nephropathies

Immune-mediated glomerulopathies can be considered as resulting from inappropriate activation of the immune response, followed by an inflammatory reaction similar to that associated with an appropriate immune response or with allograft rejection (Fig. 1). Inflammation can be triggered by activation of the complement cascade or by T cell activation and involves the recruitment of macrophages, lymphocytes, fibroblasts, and myofibroblasts as well as proliferation of mesangial cells (Fig. 1). Because immune activation under these circumstances is essentially inexhaustible, the process extends indefinitely, leading to progressive destruction of nephrons, which become replaced by fibrous tissue.

As in allograft rejection, the strategy aimed at detaining immune-mediated glomerulopathies has con-
receiving lifelong MMF treatment, T lymphocyte activation and the production of anti-DNA antibodies were suppressed, whereas albuminuria was limited. Mortality at 60 wk of age was 90% in untreated and 0 in MMF-treated animals. Van Bruggen et al. (80) treated MRL/lpr mice with MMF. At 23 wk of treatment, proteinuria was much less frequent in treated mice than in untreated controls. Accordingly, glomerular structural injury and glomerular deposition of Ig and C3 were milder in treated than in untreated animals. In MRL/lpr mice, Yu and co-workers (84) found that MMF treatment diminished the renal cortical expression of the inducible isoform of nitric oxide (NO) synthase (iNOS), which has been implicated in the pathogenesis of renal injury in lupus nephritis. Accordingly, MMF treatment diminished the urinary excretion of NO metabolites, suggesting that overall NO production was equally reduced. In association with these effects, MMF treatment had a protective effect on the glomerular structure, limiting tuft hypertrophy and ameliorating proteinuria and glomerulosclerosis.

Several clinical studies have suggested that patients with lupus nephritis may respond favorably to MMF treatment. However, most of the studies reported to date have been either anecdotal (21, 29) or based on uncontrolled observations of adult (16, 27, 39) and pediatric (9) SLE patients. In a cohort of 42 patients with diffuse proliferative lupus nephritis, Chan and co-workers (10) compared the renal protective effect and the toxicity of a combined prednisolone and MMF treatment given for 12 mo (group 1; 21 patients) with those of an association of prednisolone and cyclophosphamide maintained for 6 mo, followed by treatment with prednisolone and azathioprine for another 6 mo (group 2; 21 patients). They found that 95% of patients in group 1 had complete (81%) or partial (14%) remission, compared with 90% (76% complete and 14% partial) in group 2. Side effects were more frequent in group 2 than in group 1. Collectively, these initial observations suggest that MMF may become a valuable alternative to conventional immunosuppressors in the treatment of lupus nephritis, especially when its relatively low toxicity is considered. However, additional controlled studies will be needed before the use of MMF in this particular clinical setting can be formally recommended.

Heymann nephritis and membranous nephropathy. Luca and co-workers (46) examined the effect of MMF in rats with active Heymann disease, a model of human membranous glomerulopathy. MMF had no effect on the glomerular deposition of IgG, although it did reduce glomerular C3 accumulation. Nevertheless, the percentage of rats that developed proteinuria in the treated groups was significantly lower than that of untreated rats. In the same model, Penny and associates (63) showed that MMF treatment started immediately after induction of the disease and maintained for 4 wk prevented glomerular Ig deposition and interstitial infiltration by T lymphocytes and macrophages, easily observed in untreated rats at 8 wk. In addition, early temporary MMF treatment completely prevented the associated massive proteinuria. These protective effects were absent when temporary MMF treatment was initiated 4, 6, or 10 wk after induction of the disease, when immune-mediated injury was already established. These observations underscore two important concepts. First, early T lymphocyte activation/proliferation is a crucial pathogenic step for the development of immune-mediated renal injury, even when the process is initiated by humoral mechanisms. Second, once set in motion, T lymphocyte-mediated injury may propagate and become autonomous. MMF monotherapy may have only limited efficacy at this phase.

There is little clinical experience with MMF in patients with membranous glomerulopathy. In an uncontrolled clinical series, Miller at al. (52) administered MMF to 16 patients with primary membranous nephropathy. There were no significant changes in mean values for serum creatinine, serum albumin, or proteinuria, although the latter fell by 50% in six patients, whereas partial remissions were observed in two patients. It must be stressed that these patients had been resistant to conventional therapy and might therefore represent a subpopulation with particularly severe and intractable disease. In another uncontrolled study, Choi and co-workers (11) treated a cohort of 46 patients who had assorted primary glomerulopathies with MMF. In those suffering from membranous glomerulopathy (n = 17), MMF reduced median proteinuria from 7.3 to 1.5 g/day and ameliorated the serum levels of albumin and cholesterol.

Other immune-mediated nephropathies. Nowack et al. (59) administered MMF combined with low-dose oral corticosteroids to nine patients with Wegener granulomatosis and two patients with microscopic polyangiitis, all of whom had severe renal involvement. In all patients, remission was achieved, with only one relapse after 14 mo. Successful MMF treatment of IgA nephritis and Goodpasture syndrome has also been reported in anecdotal form (26, 58). In the study by Choi and co-workers (11), patients with membranoproliferative glomerulonephritis and IgA nephropathy also experienced improvement with MMF treatment. A beneficial effect of MMF in Takayasu arteritis has been reported in anecdotal form (14).

USE OF MMF IN NONIMMUNE-MEDIATED NEPHROPATHIES

Pathogenesis of Nonimmune-Mediated Nephropathies

A large fraction of progressive glomerulopathies develops in the absence of any perceptible immunological derangement. This is the case with focal and segmental glomerulosclerosis (FSGS), diabetic nephropathy, and hypertensive nephrosclerosis, which collectively are thought to represent the original cause of renal injury in >80% of new ESRD cases in the US (77).

The exact mechanisms involved in the pathogenesis of nonimmune-mediated progressive glomerulopathies have not been fully elucidated, despite numerous advances obtained in the past 20 years. The immune-independent mechanism most consistently associated
with progressive nephropathies is mechanical stress to the capillary walls (7). Intracapillary hypertension and tuft hypertrophy, frequently encountered in experimental models of progressive nephropathies, can damage the glomerulus by increasing the mechanical tension applied to its walls, according to the La Place relationship (85). Several in vitro studies have indicated that mechanical strain is a powerful proinflammatory stimulus that can lead to mesangial cell proliferation, excessive production of extracellular matrix, and abnormal production of growth factors (85). These events can evolve to glomerular and interstitial inflammation (Fig. 2) that involves, as in allograft rejection and immune-mediated nephropathies, the recruitment of T lymphocytes and macrophages (18, 19, 23, 71).

In principle, renal inflammation may be initiated independently of hemodynamic stress in subjects with serious impairment of the glomerular barrier, such as in long-standing nephrotic syndrome. In these situations, the proximal tubular cells are persistently forced to absorb enormous amounts of filtered protein. The intracellular processes involved in massive protein absorption can lead to the local production of cytokines, chemokines, and growth factors, attracting inflammatory cells and eventuating in peritubular inflammation (1).

Evidence has been reported that podocyte injury can initiate glomerulosclerosis by promoting adhesion of the glomerular tuft to the parietal layer of Bowman’s capsule, as well as progressive perinephric inflammation (42). Podocyte injury can be initiated by mechanical stress, thus constituting yet another mechanism of mechanically induced glomerular damage. However, other instances have been described in which experimental podocyte injury could not be directly attributed to glomerular hemodynamic dysfunction (41), suggesting the operation of additional mechanisms. In fact, FSGS is regarded by some as a primary podocyte disease (38).

Biochemical dysfunction such as that observed in dyslipidemia and in certain hereditary diseases (Alport syndrome, Fabry disease, etc.) can also initiate inflammation and chronic renal disease. One particular biochemical abnormality, namely, the production of advanced glycation end products (AGE), has been implicated in the pathogenesis of at least two important causes of chronic renal disease, namely, diabetes and aging. AGE formation can promote glomerular injury and chronic inflammation by at least two mechanisms: 1) slow distortion of local structures by cross-linking of collagen molecules (48); and 2) activation of specific AGE receptors (RAGE), leading to the production of cytokines and enhanced synthesis of extracellular matrix components (15).

Recent evidence suggests that ANG II, once regarded as a vasoactive peptide involved solely in sodium conservation, participates actively in these inflammatory events, stimulating cell proliferation and fibrogenesis, the synthesis of chemokines and growth factors, and the recruitment of mononuclear cells (37, 72, 82, 83). Tubular or interstitial ANG II expression was found in rats with subtotal nephrectomy (28, 57) and in experimental models of hypertension (64, 70). Of note, interstitial ANG II can also be found in immune-mediated nephropathies such as experimental immune complex nephritis (72) and human allograft rejection (61), particularly at inflamed areas. Part of this anomalous ANG II production may occur in lymphocytes (64). ANG II may even function directly as a cytokine, stimulating the proliferation of T lymphocytes and enhancing cell-mediated immunity (55).

The nephron loss resulting from progressive renal injury brings additional mechanical stress to the surviving units, which must compensate for those that have succumbed, leading to further inflammation and renal injury (7). This vicious cycle perpetuates the chronic nephropathy even when the initial insult has ceased and accelerates the progression to ESRD (Fig. 2).

Thus, as illustrated in Fig. 2, the pathogenesis of nonimmune-mediated nephropathies requires the operation of an initial insult, such as glomerular hypertension or enhanced filtration of macromolecules, and of inflammatory events, which appear essential to the amplification and propagation of injury. Strategies aimed at arresting nonimmune-mediated nephropathies have been based mostly at ameliorating hemodynamic stress. This can be accomplished by administration of a low-protein diet (33, 43) and, especially, given the myriad of effects of ANG II, by treatment with suppressors of the renin-angiotensin system, such as ACEI and ANG II receptor blockers (2, 8, 44, 45, 49). However, the inflammatory component of nonimmune-

![Fig. 2. Schematic and simplified representation of nonimmune-mediated mechanisms of progressive renal injury. Asterisks represent targets for MMF action. Note the similarity to Fig. 1 regarding asterisk location.](http://ajprenal.physiology.org/)}
mediated nephropathies has also been targeted, because treatment with immunosuppressors such as cyclophosphamide and azathioprine has been given, with variable success, to patients with nonimmune-related nephropathies such as FSGS. Given the apparent pathogenic importance of inflammatory events in non-immune-mediated nephropathies, the use of an immunosuppressor with low toxicity such as MMF appears in order, as represented by the asterisks in Fig. 2, which are distributed in a similar manner as in Fig. 1. The following paragraphs will discuss the evidence that the use of MMF in nonimmune-mediated nephropathies is indeed warranted.

**Beneficial Effects of MMF in Nonimmune-Mediated Nephropathies**

The 5/6 renal ablation model. The 5/6 renal ablation model (Nx), used mostly in rats, can be regarded as a typical instance of nonimmune-mediated chronic nephropathy. In these animals, renal injury is initiated by glomerular hypertension/hypertrophy but likely is amplified and propagated by inflammatory mechanisms (Fig. 2). Fujihara, Noronha, and co-workers (23, 57) administered MMF to Nx rats, starting immediately after renal mass removal. MMF strongly attenuated the early lymphocyte and macrophage infiltration observed in the renal tissue of these animals but had no effect on glomerular hypertension or hypertrophy. In addition, MMF reduced the number of interstitial cells staining positively for ANG II. Sixty days after renal ablation, albuminuria, glomerulosclerosis, and interstitial fibrosis were evident in untreated rats. MMF largely attenuated glomerular and interstitial fibrosis without reducing proteinuria. In a similar and almost simultaneous study, Romero and co-workers (71) confirmed the protective effect of MMF regarding glomerulosclerosis, interstitial injury, and the antecedent lymphocyte/macrophage infiltration. In addition, they showed that MMF treatment reduced the expression of lymphocyte adhesion molecules, which helps to explain the reduced inflammation observed in MMF-treated rats. Badid and collaborators (4) showed that MMF reduced infiltration by myofibroblasts and expression of collagen III in the renal tissue of Nx rats. In addition, MPA dose dependently inhibited the in vitro proliferation of rat fibroblasts. Again, all of these effects were associated with attenuation of the structural and functional changes associated with the Nx model.

**Experimental models of hypertension.** Rats subjected to chronic NO inhibition develop systemic hypertension, which is accompanied by severe renal injury, consisting of proteinuria, glomerular sclerosis, glomerular collapse, interstitial fibrosis, and vascular damage (5, 68). These abnormalities are aggravated by simultaneous administration of dietary salt overload (24). Fujihara et al. (22) showed that rats receiving a NO inhibitor and a salt-rich diet develop severe glomerular hypertension as well as renal lymphocyte/macrophage infiltration, particularly at the interstitial area (62). Treatment of these rats with MMF limited renal interstitial inflammation and ANG II accumulation and attenuated glomerular and interstitial injury, without ameliorating glomerular hypertension or proteinuria. Quiroz et al. (64) showed that rats receiving a NO inhibitor during a 3-wk period became salt sensitive, developing hypertension and renal injury when challenged subsequently with a high-salt diet. However, rats receiving MMF during the NO inhibition period remained salt resistant. This protective effect of MMF was associated with its ability to prevent glomerulosclerosis and vascular damage, as well as inflammation-related events such as renal infiltration by T lymphocytes and the appearance of ANG II-positive cells. The same group examined rats given a 5-wk infusion of ANG II, which developed hypertension, tubulointerstitial injury, and renal infiltration by activated T cells, a large fraction of which stained positively for ANG II. MMF treatment limited these abnormalities and prevented the subsequent development of salt-sensitive hypertension (69). In a related study (20), it was shown that the renal vasoconstriction and glomerular hemodynamic abnormalities associated with ANG II infusion were also prevented by MMF treatment. A similar study (70) was carried in the spontaneously hypertensive rat (SHR), a model that closely mimics human essential hypertension. These investigators showed in these rats that elevated blood pressure was associated with renal infiltration by lymphocytes, macrophages, and ANG II-positive cells. Administration of MMF prevented both renal inflammation and the development of arterial hypertension. Collectively, the observations made in these experimental models indicate that renal inflammatory events are closely associated with hypertension and can be a cause and/or a consequence of the heightened blood pressure levels. Limitation of these events by anti-inflammatory therapy offers the exciting perspective of preventing both the development of hypertension and hypertensive renal injury.

**Other nonimmune-mediated models of chronic nephropathy.** Despite the growing importance of diabetic nephropathy as a cause of ESRD (77), the effect of MMF has been tested in a single study to date. Utimura et al. (79) administered MMF to uninephrectomized streptozotocin-diabetic rats, starting immediately after diabetes induction. MMF prevented renal infiltration by macrophages but not the glomerular hypertension characterized by the high blood pressure levels of diabetic rats and widespread glomerular segmental sclerotic lesions, whereas protein excretion and glomerulosclerosis were comparable in MMF-treated diabetic rats and uninephrectomized controls. These observations suggest that MMF may prevent diabetic nephropathy by limiting renal inflammation, rather than by ameliorating glomerular hemodynamics.

Ryuzo and Soares (73) examined rats with adriamycin nephropathy for 28 wk. MMF treatment attenuated the proteinuria associated with this model but failed to limit glomerular or tubulointerstitial injury at the end of the study.
Recent and still limited evidence suggests that MMF may help to prevent not only chronic but also acute renal failure. Jones and Shoskes (34) showed that MMF treatment, in association with flavonoids, prevented renal expression of chemokines, apoptosis, acute renal injury, and acute renal dysfunction in rats subjected to renal ischemia. Lui et al. (47) showed that pretreatment with MMF inhibited the renal production of NO and the renal expression of the iNOS gene in mice undergoing ischemia-reperfusion injury, consistent with the view that MMF may ameliorate these processes. Similarly, Ventura and co-workers (81) showed that MMF pretreatment attenuated early renal inflammatory signs and glomerular filtration rate depression in rats subjected to bilateral renal arterial occlusion for 60 min. By contrast, recent observations by Gonzalez and co-workers (30) suggest that MMF may actually aggravate renal injury in a model of postischemic renal failure.

Clinical studies. In their series, Choi et al. (11) examined 18 patients with focal and segmental glomerulosclerosis. After MMF treatment, median proteinuria decreased by >60%, whereas serum creatinine levels remained unchanged. Again, it must be noted that this was an uncontrolled study, although amelioration of proteinuria by MMF was very consistently observed in all groups studied.

COMBINING MMF WITH OTHER THERAPEUTIC AGENTS

The complexity of the mechanisms outlined in Figs. 1 and 2, and the consequent multiplicity of possible therapeutic interventions, prompted the hypothesis that associating MMF with other agents might protect renal tissue more effectively than MMF monotherapy. Four recent experimental studies seem to corroborate this hypothesis. Interestingly, two of these studies involved a nonimmune-mediated nephropathy (the Nx model), whereas the other two studies addressed immune-mediated models (transplant nephropathy and lupus nephritis), further illustrating the concept that immune and nonimmune nephropathies share crucial steps in the pathogenesis of progressive nephropathies. Remuzzi and associates (67) treated Nx rats with either MMF, the ACEI lisinopril, or a combined MMF-lisinopril treatment. All treatments were started 7 days after renal ablation. In untreated Nx rats, proteinuria and renal structural injury were associated with renal interstitial infiltration by macrophages, lymphocytes, dendritic cells, and cells expressing major histocompatibility complex II antigen. As expected, lisinopril treatment substantially limited the development of proteinuria and renal structural damage, although glomerular and interstitial injury were not completely prevented. Of note, lisinopril treatment markedly attenuated interstitial infiltration by inflammatory cells, including dendritic cells and major histocompatibility complex II-positive cells. Unlike the results obtained with MMF therapy started immediately after ablation (23), MMF initiated at day 7 failed to reduce renal injury and only partially prevented renal inflammation. Combined MMF-lisinopril therapy provided more effective renal protection than the respective monotherapies, nearly completely preventing interstitial inflammation, proteinuria, and glomerulosclerosis. Fujihara et al. (25) treated Nx rats with either MMF, the ANG II receptor blocker losartan, or a combined MMF-losartan regimen. All treatments were started 30 days after renal ablation, when renal injury was already established. Losartan treatment attenuated renal macrophage infiltration but only partially prevented the progression of proteinuria and structural injury. Again, late MMF treatment was far less effective than when initiated immediately after ablation, whereas combined MMF-losartan treatment reversed hypertension and proteinuria and arrested the progression of renal injury. The superiority of combination treatments was further stressed by two other studies by Remuzzi and associates (67). In a rat model of renal transplantation, Noris et al. (56) showed that the association of MMF and losartan provided better protection from graft inflammation and structural injury than treatment with either agent alone. Combination therapy was also more effective in arresting graft nephropathy than treatment with cyclosporin. Zojia et al. (88) obtained amelioration of murine lupus nephritis using single therapy with either MMF or a cyclooxygenase inhibitor. Combining the two agents afforded better protection than any of the individual agents alone.

No clinical studies have compared the efficacy of MMF as a single drug with that of its association with other therapeutic agents. However, it must be stressed that in several studies MMF has already been used in association with other immunosuppressors such as calcineurin inhibitors.

EARLY VS. LATE MMF TREATMENT

The findings described in several studies (25, 63, 67) indicate that to exert effective renal protection, MMF treatment must be instituted early in the course of the nephropathy, because starting it after the disease is established substantially decreases its efficacy. The reason for this discrepancy is unclear. As noted above, lymphocyte proliferation and increased expression of adhesion molecules are early events in both immune-mediated and nonimmune-mediated nephropathies. For this reason, the impact of MMF treatment is likely strongest early in the course of the disease. If initiated at later stages, when other cellular events acquire greater pathogenic importance, MMF can still exert a protective effect but requires the association of agents with complementary mechanisms of action, such as ACEI. Because late treatment is far more common in clinical practice, these combined regimens may become an important therapeutic option in the management of these processes.

UNTOWARD EFFECTS OF MMF THERAPY

As with other immunosuppressors, MMF may increase the susceptibility to infections, especially by cytomegalovirus (74, 76, 78). In addition, MMF may
favor the appearance of lymphomas in a small percentage of patients (78). Recent evidence indicates that the antiproliferative effect of MMF may impair wound healing after surgery (87) and, as mentioned earlier, may aggravate postischemic acute renal failure (30). Other common untoward effects include reversible diarrhea, leukopenia, and hair loss (16). Nevertheless, the overall toxicity of MMF is generally regarded as substantially lower than that of other commonly employed immunosuppressors (51).

CONCLUSIONS

Growing evidence indicates that inflammatory events play an important role in the development of immune-mediated and nonimmune-mediated chronic nephropathies and that immunosuppressors with low toxicity such as MMF may become extremely useful in the management of these processes. Large clinical studies will be necessary to establish whether the use of MMF, alone or in combination with other drugs, will become part of the routine treatment of progressive nephropathies.

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