Mycophenolate mofetil alleviates persistent proteinuria in IgA nephropathy

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Background. Mycophenolate mofetil (MMF) is increasingly used to treat primary glomerulopathies. Its effectiveness in IgA nephropathy (IgAN) remains unclear.

Methods. Forty IgAN patients with persistent proteinuria (>1 g/24 hours) despite conventional treatment with blockers of the renin-angiotensin system were randomized to receive MMF for 24 weeks (group 1) or continue conventional therapy (group 2), and followed for 72 weeks. The primary end point was reduction of proteinuria by 50% or more over entry level.

Results. Sixteen patients (80%) in group 1 versus six patients (30%) in group 2 reached the primary end point (P = 0.0019). Time-averaged change in proteinuria showed a significant decline in group 1, while control subjects displayed a modest rise (P = 0.003). By 72 weeks, the mean proteinuria was 62.0 ± 7.7% (P = 0.003) and 120.5 ± 14.1% (P = 0.351) that of the corresponding baseline value in group 1 and group 2, respectively. There was concomitant increase in serum albumin and decrease in serum IgA levels in group 1 but not group 2 patients. Baseline histologic grades, blood pressure control, and the rates of change in serum creatinine and creatinine clearance were not different between the two groups. Normalization in binding of polymeric IgA to cultured mesangial cells and serum interleukin-6 (IL-6) levels, which sustained to study end, was observed in group 1 but not group 2 subjects.

Conclusion. In selected patients with IgAN, MMF is effective in lowering proteinuria and ameliorating some of the putative pathogenetic abnormalities.

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide [1]. The glomerulopathy usually runs an indolent but slowly progressive course leading to end-stage renal failure in 20% to 50% of patients over 30 years. Given its complex and as yet incompletely understood pathogenetic mechanisms, there is to date no curative therapy for patients with IgAN. Most clinicians employ blockers of the angiotensin system, such as angiotensin-converting enzyme (ACE) inhibitors or, more recently, angiotensin II receptor blockers (ARBs) for control of hypertension and proteinuria. However, many patients remain significantly proteinuric despite treatment with angiotensin blockade. Although fish oil supplementation was once thought to be a promising therapeutic agent for patients with proteinuria of over 1 g/24 hours [2], its therapeutic value was not reproducible in Chinese subjects with IgAN [3]. Moreover, a recent meta-analysis [4] has cast doubt on the putative benefit of fish oil supplementation in IgAN.

The predominant glomerular deposition of abnormally glycosylated polymeric IgA and the frequently elevated circulating IgA levels in primary IgAN [5] suggest a pathogenetic role for deranged antibody synthesis. Mycophenolate mofetil (MMF) acts by releasing mycophenolic acid that selectively suppresses the proliferation of T and B lymphocytes, antibody formation, and the glycosylation of adhesion molecules through inhibition of de novo guanine nucleotide synthesis [6]. In clinical trials, MMF proved to be efficacious for the prophylaxis of renal allograft rejection [7] and for the treatment of severe lupus nephritis [8] with a favorable safety profile. Furthermore, MMF has been anecdotally reported to avert progression to allograft failure in recurrent IgAN of the transplanted kidney [9]. Here, we evaluated the efficacy of MMF in reducing proteinuria in patients in whom significant proteinuria persists despite treatment with angiotensin blockade.

METHODS

This was a prospective, randomized, controlled trial performed in two major regional renal centers in Hong Kong to test the hypothesis that MMF will lead to a significant and sustained decline in proteinuria in patients with
IgAN and persistent proteinuria despite adequate treatment with blockers of the angiotensin system, compared to a control group of patients receiving comparable doses of angiotensin inhibition without MMF. The study was approved by an Institutional Review Board and Ethics Committee of the Hong Kong Hospital Authority, and all participating patients gave written, informed consent.

**Patient selection**

Patients of either gender were eligible if they had histologically confirmed IgAN and clinically significant proteinuria of over 1 g/24 hours on three or more consecutive measurements 4 to 6 weeks apart despite adequate blockade of the angiotensin system, which refers to treatment with an ACE inhibitor, or an ARB if the patient was intolerant to the former, for at least 6 months to achieve a target blood pressure of <125/85 mm Hg. This level of proteinuria was chosen as urine protein excretion of >1.0 g/24 hours has been shown to be strongly associated with subsequent development of renal failure in IgAN [10]. Patients with glomerulopathies other than IgAN, serum creatinine over 300 µmol/L (3.4 mg/dL), systemic infection or malignancy, and women of child-bearing age who were pregnant, lactating, or unwilling to practice reliable contraception, were excluded.

All patients were instructed by a dietician to have a sodium-restricted diet of 50 mmol/day, and regularly followed by the same dietician who would obtain full dietary history, reiterate the need to control salt intake, and answer any queries about different types of diets during each visit. Dietary compliance was checked by evaluating urinary excretion of sodium every 8 weeks during follow-up. Due to the large variety of the Chinese diet, sodium excretion rates not exceeding 80 mmol/24 hours were considered acceptable.

**Histologic assessment**

The histologic diagnosis of IgAN was based upon the demonstration of mesangioproliferative changes on light microscopy and the concomitant presence of predominant or codominant mesangial deposition of IgA. Histologic grading of all renal biopsy samples were determined by a central pathologist in accordance with the classification published by Haas [11]. Patients with minimal or no mesangial hypercellularity (Haas subclass 1) or advanced glomerulosclerosis and tubular atrophy (Haas subclass 5), were excluded. To provide information on prognosis, the biopsy samples were also graded with respect to the extent of glomerular sclerosis, tubular loss, interstitial fibrosis, and hyaline arteriolosclerosis, in accordance with the method developed by To et al [12], who showed that glomerular sclerosis represents the most important prognostic factor in adult patients with primary IgAN and has a strong predictive value for renal survival.

**Study design**

Eligible subjects were randomly assigned to receive MMF (2 g/day if body weight was ≥ 60 kg, or 1.5 g/day if body weight was <60 kg) in addition to concurrent medications (group 1), or to continue contemporaneous medications without addition of MMF (group 2). The rationale of choosing this dosing regimen stems from our experience in Chinese renal transplant recipients in whom complications such as diarrhea and anemia are more prevalent in those who receive MMF 2 g/day and have body weight below 60 kg. The dose of either ACE inhibitor or ARB was titrated to reach the target blood pressure of <125/85 mm Hg. Blood pressures were recorded as the mean of three morning measurements (to the nearest 2 mm Hg). The first line ACE inhibitor used was lisinopril or enalapril. The first-line ARB used was losartan. Additional antihypertensive drugs using the nondihydropyridine calcium channel blocker diltiazem and other drugs were allowed, at the attending physician’s discretion, if target blood pressure was not achieved despite maximum dose of ACE inhibitor or ARB. None of the patients were given ACE inhibitor/ARB combination.

Upon study entry, full medical histories and physical findings were documented. Baseline investigations included full blood count, liver and renal biochemistries, 24-hour urine protein excretion, creatinine clearance rate, serum IgA level, plasma total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol, and plasma triglyceride levels. Patients were followed initially at 2-week intervals for the first month, then at 4-week intervals until 48 weeks. Thereafter, the follow-up interval was 8 weeks until study end. At each clinic visit, blood pressure, body weight, blood count, renal function, 24-hour urine sodium, protein, and creatinine clearance were monitored. Serum IgA level and lipid profile was measured at weeks 24, 48, and 72. To reduce variability, all assays were performed at a single central laboratory using standard methods. In addition, circulating IgA was isolated from all patients at baseline, weeks 24, 48, and 72 for assay of its binding to cultured human mesangial cells. Serum interleukin-6 (IL-6) concentration was also determined at these time points. After 24 weeks, MMF was discontinued in group 1 patients, who were followed for a further 48 weeks off MMF, while group 2 patients continued contemporaneous medications. The entire study duration for both groups of patients was 72 weeks.

Complete remission of proteinuria was defined as a value for urinary protein excretion that was below 0.3 g/24 hours; partial remission was defined as a decline in urinary protein excretion by 50% or more over baseline value but the amount of proteinuria was over 0.3 g/24 hours. Treatment failure was defined as persistence of urinary protein excretion that exceeded 50% of the baseline value.
Gastrointestinal upset or diarrhea in group 1 patients was first treated by increasing the dosing interval of MMF (e.g., from 1 g twice a day to 500 mg four times a day), followed, if symptoms persisted, by reducing the dose of MMF by 50% and then gradually increasing it. For patients who developed anemia (hemoglobin concentration decreased to less than 10 g/dL), the dose of MMF was halved and then titrated such that hemoglobin concentration was no less than 10 g/dL.

Study end points

The incidence of remission of proteinuria (complete or partial) was the primary end point with respect to efficacy in this study. The rationale for using proteinuria reduction instead of progression to end-stage renal disease (ESRD) as the primary outcome measure is twofold. First, there is now a large body of recent evidence that implicates the deleterious effect of proteinuria per se on renal function [13–17], and that lowering proteinuria in patients with diabetic and nondiabetic glomerular diseases is associated with long-term preservation of renal function [18–20]. Second, because of the lengthy time span (typically over 15 to 20 years) for patients with relatively normal or slightly impaired renal function at disease onset to progress to ESRD, it was conceivable that the likelihood of detecting significant intergroup differences in glomerular filtration rate (GFR) within the study period was remote. Secondary end points included changes in mesangial binding of serum IgA, serum IL-6 levels, adverse effects (anemia, diarrhea, and infection), doubling of serum creatinine or ESRD, and changes in peripheral blood lymphocyte count, creatinine clearance, and serum IgA levels.

Determination of mesangial binding of serum IgA

Polymeric IgA (pIgA) from patients with IgAN had increased binding to cultured human glomerular mesangial cells [5]. Here, we studied the effect of MMF treatment on this binding property at baseline, weeks 24, 48, and 72. The binding properties of pIgA isolated from 15 normal healthy control subjects were also determined for comparison. The minimal detection limit of IL-6 was 1.6 pg/mL with intra- and interbatch precision of 3.2% and 5.2%, respectively.

Statistical analysis

Our crude estimate indicated that the enrollment of 36 patients will achieve 80% power to detect a 50% difference in the final urine protein excretion between MMF-treated and control subjects with a significance level (α) of 0.05 using a two-sided Mann-Whitney test. Assuming a dropout rate of 10%, the study was designed to enroll 40 patients.

Data are presented as means ± standard error of the mean (SE). The main efficacy analysis was performed on an intention-to-treat basis and included patients who underwent randomization. Continuous characteristics at the start of treatment were compared with Wilcoxon rank sum tests. Categorical groups were compared by the chi-square test and Fisher’s exact test, as appropriate. The cumulative percentage of patients who achieved remission of proteinuria was calculated with the Kaplan-Meier method, and comparisons between groups were made with the log rank test. Differences between study entry and study end in each group were tested by Wilcoxon signed rank test. Change in proteinuria over time between the two groups was compared using multivariate analysis of variance (ANOVA) for repeated measures with adjustment for baseline variations. Linear regression analysis was used to estimate the annual rates of change in serum creatinine concentration and creatinine clearance in each group, and the Mann-Whitney U test was used to compare intergroup differences. A two-tailed P value of less than 0.05 was taken as the level of significance.
RESULTS

Between July 2001 and December 2003, we enrolled 40 Chinese patients into the study, with 20 in each arm. The design of the study and patient recruitment process is shown in Figure 1. Baseline demographic and clinical characteristics (Table 1), as well as histologic grading (Table 2), were similar between the two groups. All group 1 patients completed the 24 weeks of MMF treatment, and all patients in both groups completed the entire 72-week study period.

Urine protein excretion

Over the 18-month study period, a total of 22 patients (16 patients in group 1 vs. 6 patients in group 2) \((P = 0.0019)\) had remission of proteinuria (Fig. 2). In group 1, four and 12 patients achieved complete \((<0.3 \text{ g/24 hours})\) and partial \((\geq 50\% \text{ decline over baseline})\) remissions, respectively. Over 62\% \((N = 10)\) of these remissions occurred during the initial 24 weeks of MMF treatment, and all patients in both groups completed the entire 72-week study period.

Changes in blood counts

Peripheral blood lymphocyte count during the initial 24 weeks dropped progressively in group 1, but not group 2, patients (Fig. 4). The mean percentage change at week 24 was significantly greater in MMF-treated versus control patients \((-22.5 \pm 3.9 \text{ vs. } +0.5 \pm 4.5\%)\) \((P < 0.001)\). Lymphocyte count in group 1 patients rebounded to pretreatment levels within 4 weeks of discontinuing MMF. There was no appreciable change in neutrophil count throughout the study. Hemoglobin fell by a mean of 0.9 \pm 0.25 g/dL at the end of MMF treatment \((P = 0.002)\) and returned to baseline levels 12 weeks later in group
1 patients, but was unchanged in group 2 patients (data not shown).

Changes in serum IgA and biochemistries

The mean serum IgA concentration decreased from 10.9 ± 3.9 mg/dL at baseline to 9.14 ± 5.0 mg/dL at the end of MMF treatment (P = 0.001), and 9.14 ± 5.0 mg/dL at weeks 28 and 72 (P = 0.003 for both time points) in group 1 patients, but was unchanged in group 2 patients.

Though three patients (15%) in the control group versus one patient (5%) in the MMF group experienced a 50% or more increase in serum creatinine levels, there was no difference in the overall rates of change in serum creatinine and creatinine clearance between the two groups over the study period (Fig. 5). The median change in serum creatinine was −0.013 mg/dL/year in the MMF group and +0.108 mg/dL/year in the control group (P = NS). There was no appreciable change in plasma lipids in both groups (data not shown).

Blood pressure changes and urinary sodium excretion

All subjects achieved target systolic and diastolic blood pressures upon study entry (Table 1). The number of subjects receiving an ACE inhibitor vs. ARB was 16:4 in group 1, and 14:6 in group 2. Six subjects in group 1 and eight subjects in group 2 required additional antihypertensive agents: four required one additional drug and two required two additional drugs in group 1, while the corresponding numbers for group 2 are five and three, respectively. Throughout the study the average systolic blood pressure was 122 ± 4 mm Hg and the average diastolic blood pressure was 71 ± 2 mm Hg in group 1; the corresponding values in group 2 were 127 ± 4 mm Hg and 72 ± 3 mm Hg, respectively (P = NS for comparisons of systolic and diastolic blood pressures between groups). Blood pressure levels did not change significantly in both groups throughout the entire study duration (Fig. 6).

All patients complied with dietary sodium restriction and urine sodium excretion rates achieved the target of being less than 80 mmol/24 hours throughout the study period (Fig. 7).

Mesangial binding of pIgA and serum IL-6 concentration

Mesangial binding of pIgA and serum IL-6 concentration was determined in group 1 and group 2 patients, as well as in 15 normal healthy volunteer subjects. The
mesangial binding of pIgA isolated from both group 1 and group 2 patients at baseline was significantly higher than that from healthy controls. In MMF-treated IgAN patients, the binding was reduced to levels comparable to those of healthy control subjects after 24 weeks of treatment, and remained at this low level for a further 48 weeks after MMF was withdrawn. Mesangial binding in control IgAN patients showed an initial decrease, but remained significantly higher than that of MMF-treated patients and healthy control subjects at 24 weeks and beyond (Fig. 8A).

Serum IL-6 concentration in both groups of patients was significantly higher at baseline than that of healthy controls. At weeks 48 and 72, serum IL-6 concentration dropped to levels comparable to those of healthy subjects in group 1, but remained unchanged in group 2 (Fig. 8B).

**Side effects**

MMF was well tolerated. None of the patients required drug discontinuation or had any adverse event that warranted hospitalization. All patients completed the
24-week course of MMF. Twelve subjects with body weight over 60 kg were prescribed 2 g/day, while the remaining were given 1.5 g/day. Three patients developed a fall in hemoglobin level to below 10 g/dL that improved after dose adjustment during the first 4 weeks (2 from 1.5 g/day to 1 g/day, and 1 from 2 g/day to 1.5 g/day). One of the anemic patients also developed diarrhea, and another patient experienced transient upper gastrointestinal upset. There were a total of three infective episodes (two of urinary tract infection, and one of cervical lymphadenitis) in two group 1 patients, and all responded to simple oral antibiotic treatment. No adverse event was documented in group 2 patients.

DISCUSSION

In addition to its established benefits in solid organ transplantation, emerging data in recent years show that MMF may hold promise for the treatment of a variety of primary glomerulopathies [22, 23]. The rationale for employing MMF to treat IgAN, a disorder believed to be immune-mediated and result from aberrant synthesis of the IgA molecule [24] stems from its selective suppressive effects on lymphocyte proliferation and antibody formation [6]. In a recent trial, Maes et al [25] reported from Belgium no benefit in 21 patients who received MMF versus 13 patients given placebo for 3 years. Only patients with histologic unfavorable criteria,
These beneficial effects, as opposed to the negative results reported by other groups [25] [abstract; Frisch G, et al, J Am Soc Nephrol 14:753A, 2003] likely result from our selection of patients with less advanced disease, as reflected by their histologic grades. Unfavorable prognostic indicators in IgAN include proteinuria >3g/day, hematuria, male gender, age, and crescents in renal histology [27]. Current clinical and experimental evidence [28–30] support the view that antiproteinuric and immunosuppressive treatment should be administered at an early phase of disease, well before histologic damage becomes irreversible, in order to achieve renal protection. Although most of the MMF-treated patients achieved only partial remission of proteinuria in our relatively short-term study, its long-term impact on renal survival could be potentially far-reaching as proteinuria reduction has been independently shown by various investigators to correlate with preservation of renal function [18–20]. Recent post hoc analyses from the RENAAL [31] and REIN [32] trials, for instance, have confirmed that reduction of albuminuria during the first 6 months of antiproteinuric treatment was associated with a reduced rate of GFR decline and risk of developing renal end point (ESRD) during long-term follow-up in diabetic and nondiabetic subjects, respectively. Reduction of proteinuria by ≥30% at 6 months was a favorable determinant of renal outcome (with significantly reduced hazard ratios for doubling of serum creatinine and ESRD) at 4 years [31]. The potential significance of partial remission of proteinuria is further supported by observations in other forms of primary nephropathy. Troyanov et al [33] recently reported partial remission as an important therapeutic target and prognostic indicator in idiopathic membranous nephropathy.

Indeed, proteinuria itself should now be considered a chief therapeutic target in glomerulopathies. In addition to clinical evidence, we and others have shown that abnormal protein trafficking may cause renal injury dose-dependently through the induction in renal tubular cells of a variety of proinflammatory and profibrotic cytokines, notably complement C3, monocyte chemoattractant protein-1 (MCP-1), IL-8, fibronectin, macrophage migration inhibitory factor [13–17], and more recently transforming growth factor-β (TGF-β) and its surface receptor [34, 35]. These cytokines in turn stimulate interstitial leukocyte infiltration, inflammation, and ultimately, scarring and loss of renal function. Thus, it is conceivable that excessive intrarenal protein trafficking may give rise to lymphocyte-mediated renal injury that, when uncontrolled by conventional antiproteinuric therapy, can be further inhibited by concomitant immunosuppression with MMF.

Although there was no demonstrable difference in the rates of change in serum creatinine and creatinine clearance over the study period between the two groups, this is not unexpected as renal failure in IgAN typically takes 15 to 30 years to develop from disease onset [36]. As such,
Fig. 8. Binding to cultured mesangial cells by polymeric IgA (pIgA) isolated from patients and healthy subjects (A), and serum interleukin-6 (IL-6) concentration in patients and healthy subjects (B). (A) Polymeric IgA was isolated from IgA nephropathy (IgAN) patients at baseline, weeks 24, 48, and 72, and its binding to cultured glomerular mesangial cells was determined by flow cytometry and expressed as mean fluorescent intensity (MFI). The binding of pIgA isolated from 15 healthy volunteer subjects was also determined for comparison. *P < 0.001; †P = 0.028; ‡P = 0.016 vs. healthy subjects; §P = 0.002 vs. baseline; #P = 0.05; ¶P = 0.004; II P = 0.047 vs. corresponding time points in group 2 (control IgAN subjects). Error bars are means ± SE.

(B) Serum IL-6 concentration was assayed at baseline, weeks 24, 48, and 72. The mean serum IL-6 level (3.61 ± 0.5 pg/mL) of the 15 healthy volunteer subjects was also determined for comparison. *P < 0.001; †P = 0.005; ‡P = 0.041; **P = 0.048 vs. healthy subjects; §P = 0.003 vs. baseline; #P = 0.005; ¶P = 0.008 vs. corresponding time points in group 2 (control IgAN subjects). *P < 0.001; †P = 0.005; ‡P = 0.04 vs. healthy subjects. Error bars are means ± SE.

It will be difficult for any short-term study, including the present study, to detect significant differences in GFRs. Indeed, another randomized controlled trial of MMF in IgAN is currently under way in North America [37]. Similar to our report, the trial is also designed to explore the clinical efficacy of MMF, to be given for 12 months followed by a year of follow-up off study drug, in reducing proteinuria in IgAN subjects with significant proteinuria despite treatment with an ACE inhibitor and fish oil supplementation for 3 months. The primary end point will be change in urine protein-to-creatinine ratio. We are not aware of any ongoing trial of MMF that employs renal survival in terms of either doubling of serum creatinine or progression to ESRD as the primary outcome measure.

In addition to proteinuria, lymphocyte count and serum IgA levels were also suppressed during MMF treatment. Interestingly, while lymphocyte count predictably returned to pretreatment levels after MMF was discontinued, serum IgA remained lower, albeit to a modest degree, than pretreatment levels at 48 and 72 weeks. The sustained lowering of serum IgA may be related to the
fact that MMF selectively inhibits proliferation of activated lymphocytes, which become inactivated, and is consistent with the capacity of MMF to block antibody formation by activated B lymphocytes in both human and murine systems [38]. Recent data from our laboratory and others suggest a structural aberration of the IgA molecule in IgAN that may exert pathophysiologic effects on target cells [39–41], reduce clearance of IgA-immune complexes [41, 42], or favor mesangial trapping of immune complexes [5, 21]. Thus, it is possible that even small reductions in IgA production by B lymphocytes as a result of purine nucleotide depletion through MMF administration could lead to overall attenuation of glomerular injury in IgAN. The validity of such contention requires further studies.

From a mechanistic viewpoint, we have previously demonstrated in vitro that the pIgA subfraction from patients with IgAN had increased binding to cultured human glomerular mesangial cells [5]. The aberrant binding properties of these antibodies could explain the characteristic observation of predominant mesangial IgA deposits in IgAN, and may provide one of the pathogenetic mechanisms for the disease. The high levels of binding observed in our patients at baseline are consistent with this finding. MMF profoundly attenuated mesangial binding of pIgA isolated from IgAN subjects to levels comparable to those from normal subjects. This low level of binding persisted after MMF was withdrawn. Besides mesangial cell binding, participation of the cytokine IL-6 is also implicated in the pathogenesis of IgAN through its role in stimulating mesangial cell proliferation and synthesis of extracellular matrix macromolecules [1, 43, 44], which are additional hallmarks of IgAN. Recent data suggest that an imbalance in serum proinflammatory cytokines, such as overproduction of IL-6, is linked to disease progression in IgAN [45]. Our finding of elevated serum IL-6 concentration compared with normal controls is consistent with the previous report of heightened IL-6 gene expression in peripheral blood T cells of IgAN subjects with proteinuria >1 g/24 hours [46]. Furthermore, a positive correlation was noted between serum IL-6 mRNA level and the quantity of proteinuria [46]. Thus, it is possible that one of the proteinuria-lowering mechanisms of MMF is mediated through suppression of IL-6 synthesis, which is consistent with its effects in suppressing other cytokines [38]. The pathogenetic role of IL-6 in IgAN is further supported by observations that suppression of IL-6 by mizoribine, a mold extract that also selectively inhibits lymphocyte proliferation, improves glomerular lesions in childhood IgAN and in ddy mice, a rodent model of IgAN [47–49]. In addition, MMF has been shown in animal models of subtotal renal ablation to possess direct anti-inflammatory and antiproliferative effects that attenuate macrophage and T-cell infiltration [50], and reduce interstitial myofibroblast infiltration and collagen deposition [51]. Furthermore, direct inhibition of mesangial proliferation may be another effect of the drug, as in vitro proliferation of human and rat mesangial cells is inhibited by MMF in a dose-dependent manner [52]. The diverse mechanisms of action of MMF are also reflected by its efficacy in glomerulopathies other than IgAN [23].

Whether the improvements in all these clinical and experimental parameters from MMF treatment may translate into a tangible advantage in overall renal outcome in IgAN requires long-term observation. Our results point to the fact that careful selection of the candidate who may benefit from MMF treatment is of fundamental importance. Patients with advanced disease may not warrant immunosuppression at all, while patients with low-grade proteinuria or those who respond to angiotensin inhibition should not be subjected to the risks of undue immunosuppression. The duration of treatment should be a delicate balance weighted between the potential risks and benefits of immunosuppressive therapy. Further investigation is needed to dissect the exact mechanisms responsible for the observed biologic effects of MMF in IgAN.

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