Long-term study of mycophenolate mofetil treatment in IgA nephropathy

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Since the efficacy of mycophenolate mofetil (MMF) to treat immunoglobulin A (IgA) nephropathy is controversial, we extended our original study by following 40 Chinese patients with established IgA nephropathy for 6 years. All patients were maintained on their angiotensin blockade medication and half were randomized to receive MMF for 6 months. After 6 years, 11 patients required dialysis (2 from the MMF and 9 from the control group). Significantly, only 3 treated (as compared to 10 control) patients reached the composite end point of serum creatinine doubling or end-stage renal disease. Linear regression showed the annualized decline in the estimated glomerular filtration rate was significantly less in the MMF-treated group. Urinary protein excretion and the albumin-to-creatinine ratio were lower with MMF treatment during the first 24 months, beyond which there was no difference between groups. Multivariable Cox regression analysis showed that the baseline estimated glomerular filtration rate and proteinuria, and change in the urine albumin-to-creatinine ratio at 1 year to be important predictors of progression to end-stage renal disease. We found that among Chinese patients with IgA nephropathy who had mild histologic lesions and persistent proteinuria despite maximal angiotensin blockade, MMF treatment may result in transient and partial remission of proteinuria in the short-term and renoprotection in the long-term.

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To date, there is no specific treatment available for immunoglobulin A nephropathy (IgAN), which remains the most common primary glomerulonephritis worldwide.[1] The predominant glomerular deposition of abnormally glycosylated polymeric IgA[2] suggests a pathogenetic role for deranged IgA synthesis. The recent discovery of the involvement of the ubiquitin–proteasome pathway in IgAN further supports an immune-mediated pathogenetic link in this disorder.[3] Mycophenolate mofetil (MMF) is a potent immunosuppressive agent which is relatively selective for lymphocytes and inhibits antibody production by B cells more than any other immunosuppressants.[4] Besides, case series suggest that MMF may be effective in reducing proteinuria in a variety of glomerular diseases, including IgAN.[5,6] So far, few randomized controlled trails have studied the role of MMF in patients with IgAN.

We have previously reported the short-term (up to 18 months) antiproteinuric effect of MMF administered for 24 weeks in a selected group of IgAN patients, namely those with persistent proteinuria despite angiotensin blockade and relatively preserved renal function and histologically mild lesions.[7] The rationale of using MMF for 24 weeks in our original study was to balance the envisaged benefits of suppressing aberrant IgA synthesis without exposing the patient to the potential side effects of prolonged immunosuppression. Conversely, several other randomized controlled trails have produced conflicting results on the efficacy of MMF in IgAN.[8–10] However, there has been no report on the long-term renoprotective potential of MMF treatment in IgAN. In this study, we report the results of an extended 6-year follow-up of our original randomized cohort of IgAN subjects who had persistent proteinuria despite adequate angiotensin blockade using either angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II antagonist.

RESULTS

Baseline characteristics

The flow diagram depicting the patient enrolment process was previously reported.[7] The baseline demographic and clinical characteristics as well as histological grading of renal biopsies, also reported previously,[7] were similar between the

Table 1 | Baseline clinical and histological characteristics of study subjects[a]

Characteristic	Group 1 (*n*=20)	Group 2 (*n*=20)
Clinical parameter		
Age (years)	42.1 ± 2.6	43.3 ± 2.8
Male/female	6:14	8:12
Number of antihypertensive drugs	1.4 ± 0.2	1.7 ± 0.2
On ACEi/on ARB	16:4	14:6
Lisinopril (dose in mg/day)	10 (16 ± 3.9)	9 (14.2 ± 5.0)
Enalapril (dose in mg/day)	6 (14.2 ± 4.9)	5 (13 ± 6.7)
Losartan (dose in mg/day)	4 (87.5 ± 25)	6 (83.3 ± 25.8)
Diltiazem (dose in mg/day)	6 (95 ± 44.2)	8 (127.5 ± 57.3)
Atenolol (dose in mg/day)	2 (50 each)	3 (75 ± 25)
Blood pressure (mm Hg)		
Systolic	120 ± 3.2	122 ± 3.2
Diastolic	74 ± 2.2	71 ± 2.6
Estimated GFR (ml/min per 1.73 m^2 BSA)[b]	52.5 ± 4.40	50.0 ± 4.51
Urine protein excretion (g/24 h)	1.8 ± 0.21	1.87 ± 0.28
Urine albumin-to-creatinine ratio (mg/mmol)	123 ± 18	127 ± 20
Histological grading		
Morphological score distribution[c]		
Grade II	5	7
Grade III	11	11
Grade IV	4	2
Prognostic score distribution[d]		
Glomerular grading (GG)		
GG 1	14	15
GG 2	6	5
GG 3	0	0
Tubulointerstitial grading (TIG)		
TIG 1	13	11
TIG 2	7	9
TIG 3	0	0
Hyaline arteriolosclerosis (HA)		
Absent	16	15
Present	4	5

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BSA, body surface area. $P>0.05$ for all comparisons between the two groups.
[a]Plus-minus values are means ± s.e. $P>0.05$ for all comparisons between the two groups.
[b]Using the abbreviated 4-variable Modification of Diet in Renal Disease study equation.[28]
[c]Determined in accordance with the classification by Haas,[26] taking into account the degree of mesangial proliferation, glomerular sclerosis, and tubular atrophy, on a scale of 1–5. Grade 1 indicates minimal histological changes, whereas grade 5 indicates advanced sclerosis and cortical tubular loss.
[d]Determined in accordance with the grading by To *et al.*[27] GG 1, mean sclerosis per glomerulus, 0 to <25%; GG 2, 25 to <50%; and GG 3, ⩾50%. TIG 1, tubular atrophy and interstitial fibrosis were absent or in an area <5%; TIG 2, 5 to <50%; and TIG 3, ⩾50%. HA was defined as the presence of arteriolar hyaline or proteinaceous exudation, with or without smooth muscle hyperplasia or luminal reduction.

two groups (Table 1). In particular, all recruited subjects had persistent proteinuria more than 1 g/24 h despite adequate angiotensin blockade.

Patient and renal survival

All group 1 patients completed the planned 6 months of MMF treatment, and all patients in both groups were followed for at least 6 years since randomization. All patients were alive at the end of the follow-up. Eleven patients (27.5%) developed end-stage renal disease (ESRD) in this cohort over the 6-year follow-up. Two (10%) patients in the

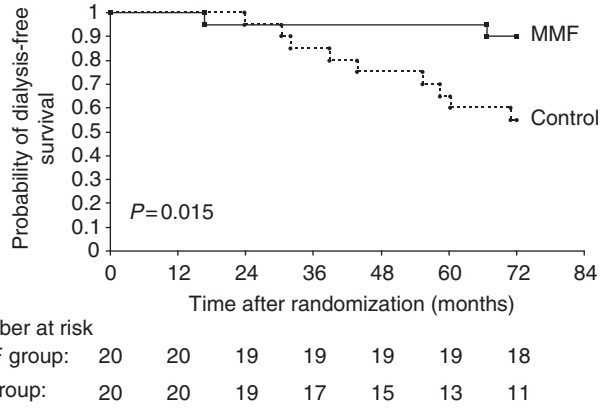

Figure 1 | Kaplan–Meier analysis of overall renal survival of 40 IgAN subjects over the 6-year follow-up period. Ctl, control; MMF, mycophenolate mofetil.

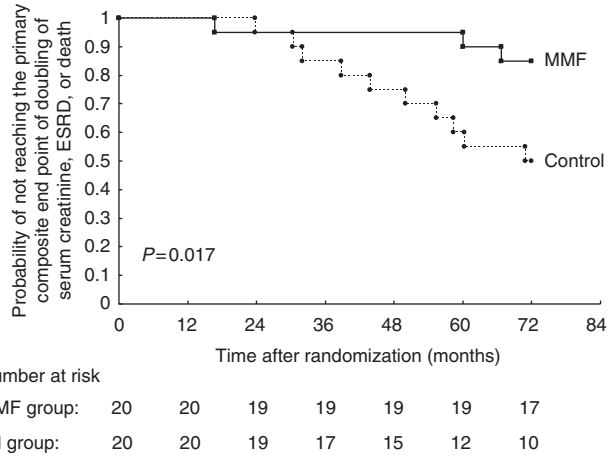

Figure 2 | Kaplan–Meier analysis of the likelihood of not reaching the primary composite end point of doubling of serum creatinine, dialysis, or death of 40 IgAN subjects over the 6-year follow-up period.

MMF group and nine (45%) patients in the control group developed progressive renal failure that required dialysis (Figure 1). Ten of these 11 patients were commenced on peritoneal dialysis, and 1 patient in the control group underwent pre-emptive renal transplantation. The 6-year renal survival was therefore 90% in MMF-treated patients and 55% in control subjects ($P=0.015$). In addition, one patient in each group had doubling of serum creatinine not reaching end-stage renal failure by the end of 6 years (Figure 2).

Urine protein excretion

Our previous report[7] suggested a modest (30% reduction from baseline) but significant difference in urine protein excretion in favor of the MMF group over the initial 18-month follow-up period. Extended follow-up showed that such inter-group difference persisted through 24 months of follow-up. However, beyond 24 through 72 months, this between-group difference in proteinuria was lost. In our

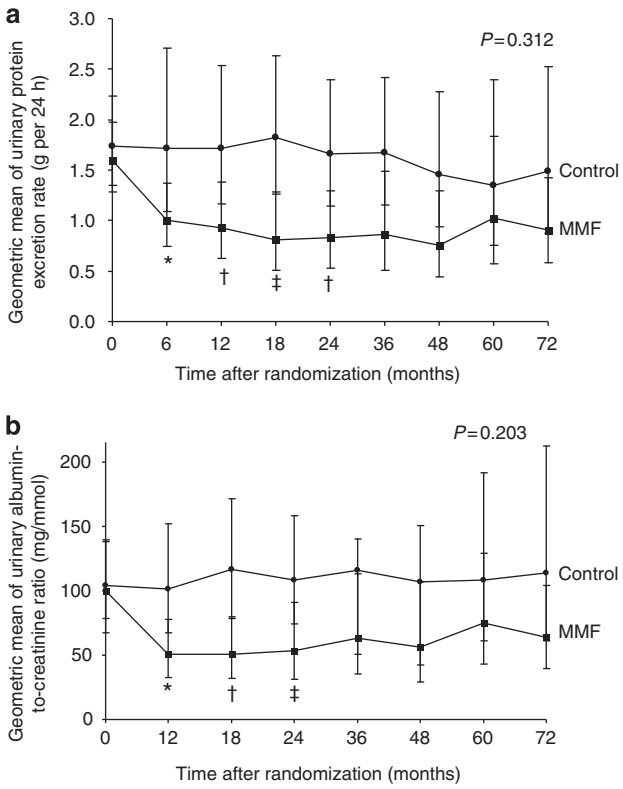

Figure 3 | Proteinuria change from baseline to study end. (**a**) Changes in urinary protein excretion during follow-up. The geometric mean values, with 95% confidence intervals, are shown. *$P = 0.019$, †$P = 0.023$, ‡$P = 0.007$ versus the control group at the corresponding time point. (**b**) Changes in urinary albumin-to-creatinine ratio during follow-up. The geometric mean values, with 95% confidence intervals, are shown. *$P = 0.019$, †$P = 0.006$, ‡$P = 0.027$ versus the control group at the corresponding time point.

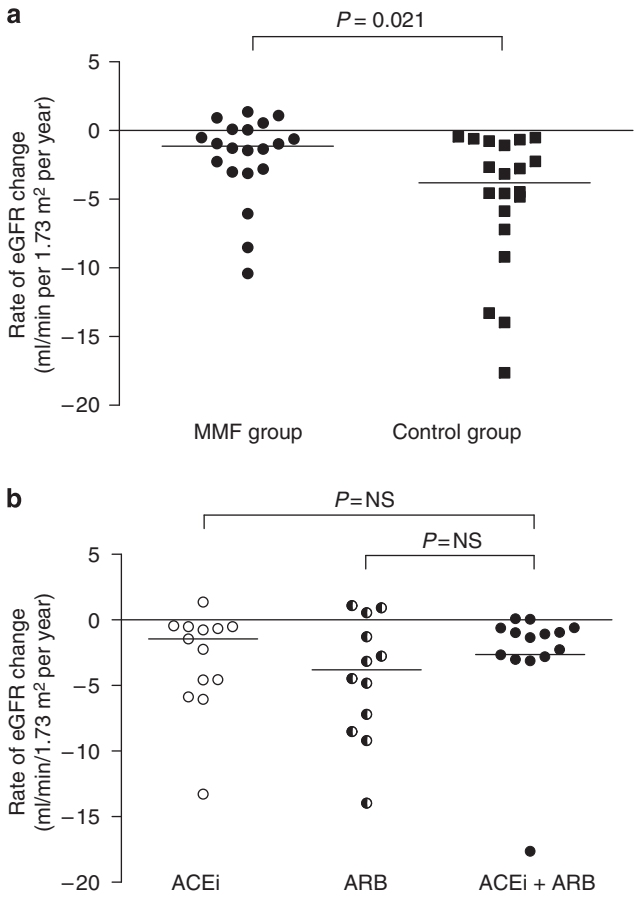

Figure 4 | Annual change in estimated GFR. (**a**) The rates of change in eGFR over the study period were calculated for each patient by linear regression analysis. The median change in eGFR, indicted by the horizontal line, was −1.125 ml/min per 1.73 m^2 per year in the MMF group and −3.812 ml/min per 1.73 m^2 per year in the control group ($P = 0.021$). (**b**) The annualized rates of change in eGFR over the study period according to the type of angiotensin blockade given: ACEi (open circle), ARB (half-filled circle), and combination (solid circle).

mixed model incorporating group, visit, and the interaction between these two factors, the overall urine protein excretion rate over the study period was not significantly better among MMF-treated versus control subjects (Figure 3a). Similarly, the urine albumin-to-creatinine ratios demonstrated the same trend (Figure 3b).

Changes in eGFR and blood pressure

The rate of estimated glomerular filtration rate (eGFR) decline over the entire follow-up duration obtained by linear regression for each patient was annualized and presented in Figure 4a. Although there was no demonstrable difference in renal function during the initial 18 months of follow-up,[7] there was a significantly more rapid eGFR decline in control subjects versus MMF-treated patients when the observation period was extended to 6 years. However, when the slope of eGFR decline was re-classified according to the type of angiotensin blockade that was given, there was no significant difference between groups (Figure 4b).

All subjects achieved target blood pressure control throughout follow-up, and there was no significant difference in systolic and diastolic blood pressures (Figure 5). The antihypertensive drugs at last clinic visit are listed in Table 2.

Predictive factors for progression to ESRD

The reduction of proteinuria at 6 months correlated significantly with the slope of eGFR against time (Figure 6). Using multivariable Cox regression analyses, baseline eGFR and change of urine albumin-to-creatinine ratio at 1-year post-randomization were predictive of ESRD or the composite end point of doubling of serum creatinine and ESRD independent of age, gender, blood pressure, and histological score (Table 3).

Adverse events

Mycophenolate mofetil was well tolerated. None of the patients required drug discontinuation. During MMF treatment, three patients developed a decrease in hemoglobin level to below 10 g/dl that improved after dose adjustment. One patient developed diarrhea, and another reported transient upper gastrointestinal upset. Three infective episodes (two of urinary tract infection, and one of cervical lymphadenitis) occurred in two MMF-treated patients, and

all responded to simple oral antibiotic treatment. No further adverse event was documented during the study after completion of MMF in the treatment group, and there was no adverse events in control patients throughout the observation period.

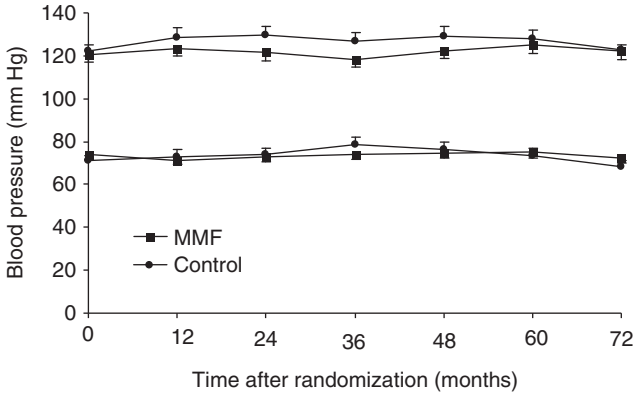

Figure 5 | Changes in systolic and diastolic blood pressure. Between-group differences for both systolic and diastolic blood pressures were not statistically significant at each time point.

Table 2 | Antihypertensive drugs at last follow-up

	MMF group	Control group
Total number of drugs	1.95 ± 0.18	1.85 ± 0.22
ACEi without ARB	4	9
ARB without ACEi	5	7
ACEi plus ARB	10	4

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MMF, mycophenolate mofetil.

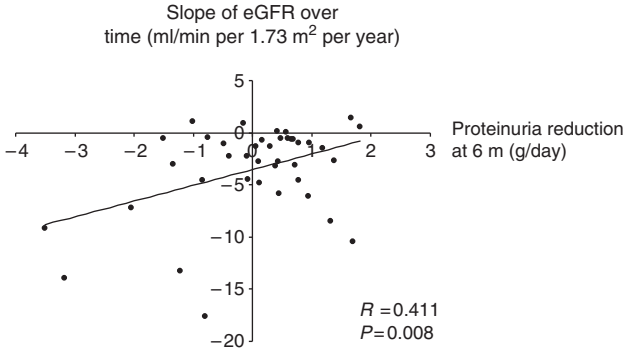

Figure 6 | Pearson's correlation between reduction in urinary protein excretion at 6 months and the slope of eGFR over time.

DISCUSSION

The use of MMF for the treatment of IgAN has been a matter of controversy in recent years. The first promising study was published in 2002 by Chen *et al.*[8] who showed that MMF administered for 12 months was more effective than corticosteroid therapy in reducing proteinuria among 62 IgAN subjects with urinary protein excretion exceeding 2 g/24 h. However, a subsequent Belgian study failed to reproduce these beneficial effects of MMF treatment. Maes *et al.*[9] reported in 2004 that MMF conferred no therapeutic benefit in 21 patients versus 13 patients administered placebo for 3 years. In this study, these investigators included only patients with histologically unfavorable criteria, hypertension, and stage 2–4 chronic kidney disease (inulin clearance 21–69 ml/min), whereas those with mild histopathological changes but heavy proteinuria were excluded. Another study from the United States reported no benefit of MMF administered for 1 year as a 'salvage' therapy in 16 patients with advanced renal insufficiency.[10] In 2005, we reported that MMF was effective in reducing proteinuria by about 30% from baseline among 40 subjects with histological mild lesions and persistent proteinuria exceeding 1 g/24 h despite maximal angiotensin blockade.[7] A recent meta-analysis[11] of these trials that yielded conflicting results concluded that MMF cannot be recommended for routine use in treating IgAN. However, all these clinical trials examined short-term outcome parameters such as proteinuria and the rate of change of GFR or serum creatinine, and long-term hard outcome follow-up data, such as renal and patient survival, are lacking. This is particularly important in IgAN that typically runs a slowly progressive and indolent course that lasts over 20–30 years.

In this study, we report the 6-year outcome in our original cohort of 40 IgAN subjects who underwent randomization. First, there was a clear renal survival advantage in patients who received MMF. The rate of eGFR decline was also lower in the MMF group over the follow-up period. Conversely, the rate of renal progression in the control group appeared faster than that would be expected for ARB-treated patients. This is not unexpected, as we only recruited subjects with persistent proteinuria over 1 g/24 h despite angiotensin blockade, which suggests that patients in whom proteinuria is resistant to angiotensin blockade may have a less-favorable prognosis. One explanation for these observations may be related to the

Table 3 | Multivariate analysis for the effect of baseline risk markers and for treatment-induced change in these markers

End point	Multivariate risk marker	Hazard ratio	95% CI	*P*-value
Renal[a]	Baseline eGFR (ml/min per 1.73 m^2)	0.92	0.88–0.97	0.001
	Urine ACR change at 1 year (g/g)	5.42	1.94–15.20	0.001
	Reduction of urine ACR (g/g)	0.18	0.07–0.52	0.001
ESRD	Baseline eGFR (ml/min per 1.73 m^2)	0.91	0.86–0.96	0.001
	Urine ACR change at 1 year (g/g)	7.65	2.17–26.9	0.002
	Reduction of urine ACR (g/g)	0.13	0.04–0.46	0.002

Abbreviations: ACR, albumin-to-creatinine ratio (each g/g equals 113 mg/mmol); ESRD, end-stage renal disease.
[a]Composite renal end point of ESRD or doubling of serum creatinine

reduction of proteinuria. In our earlier study, we demonstrated a 30% reduction of proteinuria from baseline at 18 months in MMF-treated subjects. On extended follow-up here, the inter-group difference persisted till 24 months. Thereafter, this difference in proteinuria and urine albumin-to-creatinine ratio was no longer apparent between MMF-treated and control subjects. Nonetheless, even a transient and incomplete reduction of proteinuria may be important for renoprotection, as *in vitro* and clinical studies have repeatedly demonstrated the deleterious effects of persistent glomerular proteinuria. For instance, we and others have shown that abnormal protein trafficking may cause renal injury through the induction in renal tubular cells of proinflammatory and profibrotic cytokines, notably complement C3, MCP-1, IL-8, fibronectin, macrophage migration inhibitory factor,[12–16] and transforming growth factor-β and its surface receptor.[17,18] These cytokines may in turn stimulate interstitial leukocyte infiltration, inflammation, and ultimately, scarring and loss of renal function.

Clinically, major multi-centered trials, such as the *post hoc* analyses of the RENAAL[19] and REIN[20] trials, 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 non-diabetic subjects, respectively. Reduction of proteinuria by $\geqslant$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 in diabetic nephropathy.[19] Furthermore, partial remission of proteinuria has been shown to be a positive prognostic indicator in idiopathic membranous nephropathy.[21] In this study, we showed a weak, albeit statistically significant, correlation between proteinuria reduction at 6 months and the slope of eGFR over time. Although this is in agreement with the *post hoc* analysis results of RENAAL[19] and REIN,[20] a larger cohort of study subjects is required to validate this notion in MMF-treated IgAN patients. In addition, we showed that the change in albuminuria at 1 year is strongly predictive of doubling of serum creatinine and ESRD. Our multivariable Cox regression model also showed that baseline eGFR and reduction of proteinuria on follow-up were also important predictors of subsequent renal failure, which is in keeping with prevailing data. However, histological grade and use of MMF was removed in the multivariate model, which might be related to the small patient number.

Why do Chinese and Caucasian patients have different responses to MMF treatment? Floege[22] suggested race, dose of MMF, and ACEis used might account for the differences. It must be emphasized also that in the Belgian study,[9] patients with mild histopathological changes but heavy proteinuria were excluded, which were exactly the inclusion criteria in our study. Noting the potential immunosuppressive profile of MMF, we did not want to include patients with histologically unfavorable lesions who might have been destined to progress no matter what, which probably happened in the study by Frisch *et al.*[10] At the same time, we wished to include subjects who were at risk of progression, namely, those with persistent proteinuria despite the best available antiproteinuric therapy at the time of study inception. Therefore, there appears to be a fundamental difference in patient characteristics between the Caucasian studies and the present cohort.

There are, however, several limitations of our results. First, the patient number was small to start with. This was related to the off-label use of MMF that limited our research Ethics Committee to approve the trial on a much larger scale, and the relatively high cost of the drug at the inception of the study. Nevertheless, our initial power analysis suggested that 40 subjects would have been sufficient to achieve 80% power had there been a 50% difference in the final urine protein excretion rate between MMF-treated and control subjects.[7] Although there was an overall reduction of proteinuria at 18 months' follow-up, not all patients responded in the same manner and rebound was evident after treatment cessation in some subjects on extended observation. Therefore, our small study population provides only level B evidence for the efficacy of MMF in IgAN. Larger trials are needed to yield a more definitive trend of proteinuria responses. Although the baseline characteristics were statistically similar between MMF and control groups, the randomization process resulted in a slightly higher baseline proteinuria and lower eGFR in the control group. It is possible that such subtle initial differences may be exaggerated over long periods of observation. In addition, more patients in the MMF group received combined ACEi/ARB therapy, which may have contributed to the better outcome in this group, given the antifibrotic activity of ACEi/ARB combination beyond its blood pressure and proteinuria lowering effects.[23] Although subgroup analysis by the type of angiotensin blockade did not reveal such a contention, the small patient number in each group cannot confidently exclude a type II statistical error. Finally, our results only apply to patients in whom proteinuria is not controlled despite adequate angiotensin blockade. Randomized controlled trails that include large numbers of patients of different ethnic groups are in need to answer these questions. We eagerly await the results of the North American[24] and Italian[25] trials.

PATIENTS AND METHODS

Study design and participants

Our original prospective, randomized controlled trial that commenced in year 2001–2002 has recruited 40 subjects with IgAN from two major regional renal centers in Hong Kong. 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. Patients were randomly assigned by drawing envelopes to one of two treatment groups in an open-label manner: MMF or control group.

Patients of either gender were eligible if they had histologically confirmed IgAN and clinically significant proteinuria of over 1 g/24 h on 3 or more consecutive measurements 4–6 weeks apart, despite adequate blockade of the angiotensin system using an ACEi or angiotensin II receptor blocker for at least 6 months to achieve a

target blood pressure of $<125/85$ mm Hg. Eligible subjects were randomly assigned to receive MMF (2 g/day if body weight was $\geqslant 60$ kg, or 1.5 g/day if body weight was <60 kg) for 6 months in addition to concurrent medications, or to continue contemporaneous medications without addition of MMF. Blood pressures were recorded as the mean of three morning measurements (to the nearest 2 mm Hg). Additional antihypertensive drugs were allowed to achieve blood pressure target. Patients with glomerulopathies other than IgAN, serum creatinine over 300 μmol/l (3.4 mg/dl), systemic infection or malignancy, and women of childbearing age who were pregnant, lactating, or unwilling to practice reliable contraception, were excluded.

Histological assessment

The histological 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. Histological grading of all renal biopsy samples were determined by a central pathologist in accordance with the classification published by Haas.[26] 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.*,[27] who showed that glomerular sclerosis represented the most important prognostic factor in adult patients with primary IgAN and had a strong predictive value for renal survival.

Patient follow-up

On study entry in 2002, full medical histories and physical findings were documented. Baseline investigations included full blood count, liver and renal biochemistries, 24-h urine protein excretion, urinary albumin-to-creatinine ratio, creatinine clearance rate, serum IgA level, and plasma lipid profile. At each clinic visit, blood pressure, body weight, blood count, renal function, 24-h urine protein, urinary albumin-to-creatinine ratio, and creatinine clearance were monitored. To reduce variability, all assays were performed at a single central laboratory using standard methods. After 6 months, MMF was discontinued in the treatment group. The entire study duration for both groups of patients was 6 years.

Study end points

The primary composite outcome for between-group comparison was renal survival. ESRD was defined as the need to start dialysis or undergo kidney transplantation. Secondary outcomes included changes in urinary protein excretion rate and albumin-to-creatinine ratio, and the composite end point of doubling of baseline serum creatinine, end-stage renal failure, or death.

Statistical analysis

Data are presented as means ± s.e. The main efficacy analysis was performed on an intention-to-treat basis and included all patients who underwent randomization. Continuous characteristics at the start of treatment were compared with Wilcoxon rank-sum tests. Categorical groups were compared by χ^2-test and Fisher's exact test, as appropriate. Differences between study entry and study end in each group were tested by Wilcoxon signed rank test. Cumulative renal survival was calculated with the Kaplan–Meier method, and comparisons between groups were performed with the log-rank test.

As albuminuria shows a skewed distribution in this study, averages were expressed as geometric mean. Changes in the log-transformed urinary protein excretion rate and albumin-to-creatinine ratio from baseline to months 6, 12, 18, 24, 36, 48, 60, and 72 (end point) were assessed for each time point with the Mann–Whitney *U*-test to detect inter-group differences. Treatment comparisons between the patients who did and did not receive MMF were performed with the use of a two-sided test with a significance level of 0.05. Least squares mean differences between the groups for the change from baseline in the urinary albumin-to-creatinine ratio (and associated 95% confidence intervals) were back-transformed to provide meaningful values. In addition, a mixed-effects model with the use of the appropriate procedure of the Statistical Package for the Social Sciences Inc., Chicago, IL, USA (Linear Mixed Model) was implemented to detect differences in proteinuria over time. The model included study group, visit, and the interaction term for these two factors, as well as baseline urinary albumin-to-creatinine ratio, as fixed effects and visits as repeated measurements.

Estimated glomerular filtration rate was calculated using the abbreviated 4-variable MDRD study equation, where $\text{eGFR} = 186.3 \times (\text{serum creatinine, mg/dl})^{-1.154} \times (\text{age upon follow-up, years})^{-0.203} \times (0.742 \text{ for female}) \times 1.21 \text{ for black race}$.[28] The rates of change in eGFR (slope of eGFR vs time plot) over the study period were calculated for each patient by linear regression analysis. The slope for patients who developed ESRD requiring renal replacement therapy was computed to the time point when such therapy was initiated. Inter-group differences were compared using non-parametric Mann–Whitney *U*-test. Correlation between proteinuria reduction at 6 months and the slope of eGFR over time was computed using Pearson's method. A two-tailed *P*-value of less than 0.05 was taken as the level of significance.

Factors predictive of renal failure and were identified with Cox regression analysis. Factors with $P<0.25$ on univariate analysis were entered into the multivariable Cox regression model. A backward elimination procedure with $P>0.05$ to remove was performed to identify independent predictors for the development of ESRD. To identify risk factors at baseline and treatment-induced changes in risk factors at 1 year that were independent predictors of the renal end points, baseline and baseline and change at 1-year multivariate Cox models were performed. Baseline risk factors were selected among the following covariates: age, gender, mean arterial blood pressure (diastolic blood pressure $+ 0.333 \times$ pulse pressure), eGFR, and urine albumin-to-creatinine ratio, and histologic grade using Haas classification. Risk factor for treatment-induced change analysis was change in urine albumin-to-creatinine ratio at 1-year postrandomization. All statistical analyses were performed using SPSS v.16.0 or GraphPad (GraphPad Software Inc., La Jolla, CA, USA) Prism v.5.0 as appropriate.

This trial is registered at ClinicalTrials.gov with the number NCT00863252.

DISCLOSURE

All the authors declared no competing interests.

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