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Mycophenolate Mofetil and Steroid for Treatment of Patients With IgA Nephropathy

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INTRODUCTION

IgA nephropathy (IgAN) is characterized by dominant IgA deposits in the glomeruli, with a variable clinical course, ranging from asymptomatic hematuria to rapidly progressive glomerulonephritis and even nephrotic syndrome in some instances. Up to 40% of patients ultimately progress to end-stage kidney disease.[1] To this date, the best treatment modality in the management of patients with IgAN remains unclear because of its heterogenous clinical presentation. Conservative therapy, which includes inhibition of the renin-angiotensin-aldosterone system, tight blood pressure control, cholesterol control, low salt and protein diet, and more recently SGLT2-inhibitors are now considered the mainstay of therapy in patients with IgAN. However, conservative management alone is not enough to prevent disease progression in all patients. The role of immunosuppression in patients with IgAN is less clear, especially following the results of STOP-IgA trial that suggested no benefit from adding immunosuppressive therapy to conservative management.[2] The TESTING-1 trial that did suggest benefit from use of high dose corticosteroid was terminated early because of significant concerning side effects,[3] and the TESTING-2 trial that suggested benefit for lower dose steroid in IgAN with improved side effect profile was mainly limited to patients of Chinese descent.[4] Therefore, the efficacy of immunosuppression in IgAN continues to be debated and there continues to be a search for new effective therapies. Mycophenolate mofetil (MMF) is an antimetabolite that reduces the B- and T-cell proliferation and decreases antibody production. A recent randomized clinical trial including 170 patients with progressive IgAN showed that addition of MMF to supportive care compared with supportive care alone, significantly reduced the risk of disease progression.[5]

We retrospectively evaluated the effects of combined MMF and steroid treatment versus steroid alone on incidence of kidney failure in adults with biopsy proven IgAN, compared with conservative therapy alone. The details of the study methods are shown in Supplementary Methods. This study was approved by the Mayo Clinic Institutional Review Board.

RESULTS AND DISCUSSION

A total of 166 patients were included in the final cohort for analysis (Figure 1). The overall median age at biopsy was 44 years, with 112 males (68%) and 137 Whites (85%), with a median estimated glomerular filtration rate (eGFR) of 43 ml/min per 1.73 m^2, and a median proteinuria of 1.7 g/24h. Patients were divided into 3 groups of MMF + steroid ($n = 22$), steroid alone ($n = 39$), and conservative treatment ($n = 105$). Patients were assigned to their respective groups based on what therapy they received within the first 3 months following the kidney biopsy. Patients with lower eGFR, higher degree of hematuria, and higher M, E, and C score, were more likely to have been prescribed MMF and/or steroids compared with those who were in the conservative group (Table 1). Patients were followed-up with from the time of 3 months post

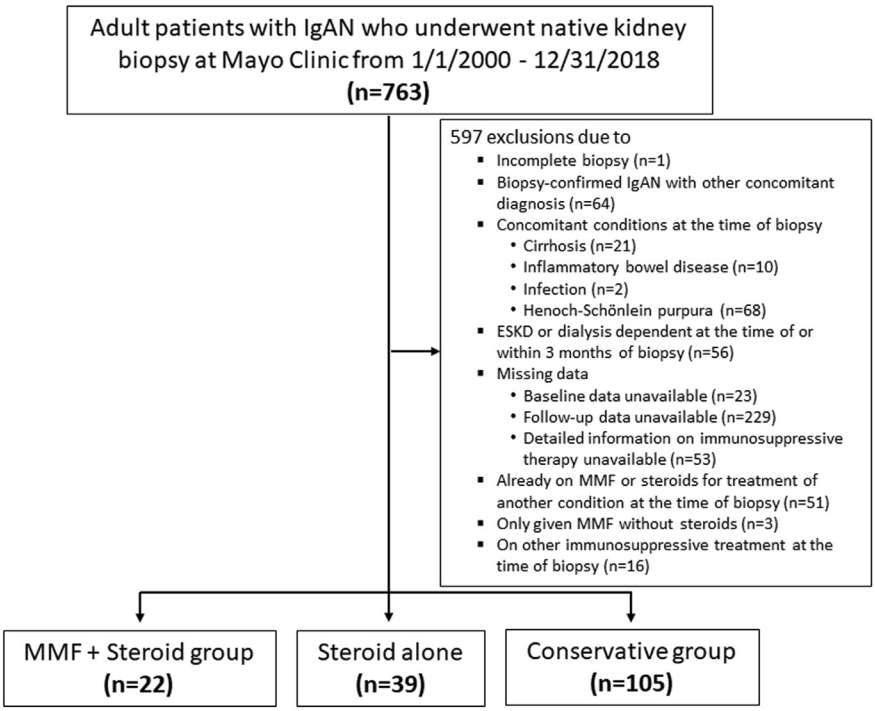

Figure 1. Flowchart of Inclusion and Exclusion Criteria for this study. ESKD, end-stage kidney disease; IgAN, IgA nephropathy; MMF, mycophenolate mofetil.

biopsy until incidence of kidney failure. Patients were censored at the time of death, last follow-up, or initiation of an additional treatment, whichever came first. A total of 30 (18.1%) patients developed kidney failure during a mean follow-up period of 6.2 years (range 1–10 years). No significant differences of renal survival were observed between groups (log-rank test: $P = 0.40$) (Supplementary Figure S1, Supplementary Table S1). However, when fitting Cox proportional hazard regression models weighted by propensity score, patients who received MMF + steroid were found to be significantly less likely to experience incident kidney failure compared with patients given conservative treatment (hazard ratio 0.12; 95% confidence interval: 0.02–0.95; $P = 0.044$), whereas patients who received steroid alone also demonstrated a decreased likelihood of kidney failure compared with those on conservative therapy, even though results were not statistically significant (hazard ratio 0.50; 95% confidence interval: 0.19–1.36, $P = 0.17$). These results are consistent with the findings from the more recent trials.[5,6] Compared with the 2 previous trials,[5,6] we had longer follow-up time (average 6 years vs. 3 years and <1 year) and longer MMF exposure time (average 23 months vs. 18 and 11 months) (Supplementary Table S2). As noted above, patients in the MMF + steroid group had lower eGFR and higher M, E, or C score at presentation and therefore the fact that they had better renal outcomes after accounting for this severe presentation suggests that the drug is effective in slowing progression. This should not be interpreted to mean that everyone with IgAN should be prescribed MMF + steroid therapy, but rather that a subgroup of patients with evidence of active inflammation (based on renal histology) would be likely to benefit from this treatment.

Our study has several strengths, notably its extended duration of follow-up, the inclusion of 3 comparison groups, and a comprehensive analysis that adjusts for pretreatment imbalances. Nevertheless, it is important to recognize certain limitations of our study, including the retrospective study design, the restriction to a single-center setting, and a relatively modest sample size. It is also imperative to emphasize that our study was susceptible to referral bias, selection bias, and a notable rate of exclusion because of missing data and the nature of Mayo Clinic as a referral center. In addition, because of sample size constraints, we were not able to incorporate all potential confounding variables into our propensity model, and so instead picked the 4 variables that were most likely to impact the decision on how to treat. We were also unable to conduct adjusted analysis for multiple comparisons within the 3 groups, primarily because of constraints imposed by the sample size and missing data.

In summary, our findings suggest that a combination therapy involving MMF and steroid holds promise as a potential treatment strategy for IgAN

Table 1. Baseline characteristics of patients with IgA nephropathy

Patient	Total (n = 166)	Conservative (*n* = 105)	Steroid alone (*n* = 39)	MMF + Steroid (*n* = 22)	*P*-Value
Age (yr)	44 [33–57]	44 [31–57]	47 [38–55]	40 [33–58]	0.47
Male sex	112 (67.5)	73 (69.5)	24 (61.5)	15 (68.2)	0.66
Race					0.30
Missing	5	3	2	0	
Non-White	24 (14.9)	16 (15.7)	7 (18.9)	1 (4.5)	
White	137 (85.1)	86 (84.3)	30 (81.1)	21 (95.5)	
Blood pressure (mmHg)[a]					
Systolic	122.9 ± 17.7	124.0 ± 18.6	122.5 ± 17.3	118.3 ± 13.6	0.48
Diastolic	76.8 ± 12.0	77.6 ± 12.6	76.6 ± 11.6	73.3 ± 8.8	0.45
Body mass index[b]	30.6 ± 9.2	30.4 ± 8.7	29.5 ± 8.6	33.9 ± 12.7	0.35
Comorbidities					
Hypertension	97 (58.4)	64 (60.9)	23 (59.0)	10 (45.6)	0.42
Diabetes	15 (9.0)	10 (9.5)	3 (7.7)	2 (9.1)	0.94
Heart failure	5 (3.0)	5 (4.8)	0	0	0.10
Serum creatinine (mg/dl)[c]	1.6 [1.2–2.1]	1.5 [1.1–2.0]	1.9 [1.4–2.3]	1.8 [1.3–2.3]	**0.005**
Estimated proteinuria (g/24h)[d]	1.7 [0.8–3.5]	1.6 [0.8–3.5]	2.3 [0.9–3.5]	1.7 [1.3–3.6]	0.50
eGFR (ml/min per 1.73 m^2)[e]	43 [31–62]	48 [33–69]	32 [29–48]	43 [26–70]	**0.005**
Degree of hematuria[f]	4 [3–6]	3 [3–5]	4 [3–8]	7 [4–8]	**0.002**
MEST-C scores (≥1)					
M	134 (80.7)	78 (74.3)	36 (92.3)	20 (90.9)	**0.022**
E	42 (25.3)	17 (16.2)	13 (33.3)	12 (54.5)	**<0.001**
S	104 (62.7)	64 (61.0)	24 (61.5)	16 (72.7)	0.58
T	62 (37.3)	38 (36.2)	16 (41)	8 (36.4)	0.86
T1	50 (30.1)	31 (29.5)	12 (30.8)	7 (31.8)	
T2	12 (7.2)	7 (6.7)	4 (10.3)	1 (4.6)	
C	41 (24.7)	13 (12.4)	16 (41)	12 (54.5)	**<0.001**

MMF, mycophenolate mofetil; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease.
[a]3 patients in the conservative group, 1 patient in the steroid alone group, and 1 patient in MMF + steroid group were missing their blood pressure value.
[b]10 patients in the conservative group, 3 patients in the steroid alone group, and 4 patients in MMF + steroid group were missing their body mass index value.
[c]1 patient in the conservative group and 1 patient in the steroid alone group were missing their serum creatinine value.
[d]3 patients in the conservative group were missing their estimated proteinuria values.
[e]6 patients in the conservative group and 3 patients in the steroid alone group were missing their eGFR values.
[f]The degree of hematuria was categorized by the number of red blood cells in urine per high power field under microscopy into D1 = 0, D2 = 1–3, D3 = 3–10, D4 = 11–20, D5 = 21–30, D6 = 31–40, D7 = 41–50, D8 = 51–100, and D9 ≥ 100 at the time of biopsy. Two patients in the MMF + steroid group, 3 patients in the steroid alone group, and 9 patients in the conservative group were missing their hematuria values.
Baseline refers to the time of biopsy. Results are presented as median [interquartile range] or mean ± SD for continuous variables and as *n* (%) for categorical variables. *P*-values for continuous variables were derived using the Kruskal-Wallis test; *P*-values for categorical variables were derived using the χ^2 test.

patients, especially those displaying active inflammation on kidney biopsy. It is important to note that our study should not be interpreted to mean that MMF + steroid should be the go to therapy for all patients with IgAN, but rather in patients with significant proteinuria and hematuria and active lesions on biopsy (with M, E, C score), treatment should be considered regardless of their S and/or T score and starting eGFR. The results of our study are ultimately applicable to the patients that were most represented in our cohort, which as a whole had a starting eGFR of median 43 ml/min with a median proteinuria of 1.7 g/24h, which places them at high risk of progression. These results should not be applied, for example, to a patient with a normal eGFR and low degree proteinuria. To definitively establish the effectiveness of MMF + steroid as a treatment for managing patients with IgAN, and to ascertain whether MMF + steroid outperforms steroid alone in treating IgAN, future investigations should prioritize randomized clinical trials and large-scale prospective studies.

DISCLOSURE

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author reasonable request to the corresponding author.

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SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Kaplan-Meier plot of renal survival in the cohort during follow-up, by treatment group.

Table S1. Probabilities of survival free of kidney failure, overall and by treatment group.

Table S2. Immunosuppressant treatment of patients with IgA nephropathy.

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