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Original Investigation

Mycophenolate Mofetil Combined With Prednisone Versus Full-Dose Prednisone in IgA Nephropathy With Active Proliferative Lesions: A Randomized Controlled Trial

Jin-Hua Hou, MD,[1,] Wei-Bo Le, PhD,[1,*] Nan Chen, MD,[2] Wei-Ming Wang, PhD,[2] Zhang-Suo Liu, MD,[3] Dong Liu, PhD,[3] Jiang-Hua Chen, MD,[4] Jiong Tian, PhD,[4] Ping Fu, MD, PhD,[5] Zhang-Xue Hu, MD,[5] Cai-Hong Zeng, PhD,[1] Shao-Shan Liang, MD,[1] Min-Lin Zhou, MD,[1] Hai-Tao Zhang, MD,[1] and Zhi-Hong Liu, MD[1]*

Background: Observational studies suggest that patients with immunoglobulin A nephropathy (IgAN) with active proliferative lesions show a good response to immunosuppressive treatment.

Study Design: Multicenter, prospective, randomized, controlled trial.

Setting & Participants: 176 patients with IgAN with active proliferative lesions (cellular and fibrocellular crescents, endocapillary hypercellularity, or necrosis), proteinuria with protein excretion ≥ 1.0 g/24 h, and estimated glomerular filtration rate > 30 mL/min/1.73 m^2.

Intervention: Mycophenolate mofetil (MMF) group: MMF, 1.5 g/d, for 6 months and prednisone, 0.4 to 0.6 mg/kg/d, for 2 months and then tapered by 20% per month for the next 4 months; prednisone group: prednisone, 0.8 to 1.0 mg/kg/d, for 2 months and then tapered by 20% per month for the next 4 months. All patients were followed up for another 6 months.

Outcomes: The primary end point was complete remission rate at 6 and 12 months.

Results: At baseline, median estimated glomerular filtration rates were 90.2 and 94.3 mL/min/1.73 m^2 and mean proteinuria was protein excretion of 2.37 and 2.47 g/24 h in the MMF and prednisone groups, respectively. At 6 months, complete remission rates were 37% (32 of 86 patients) and 38% (33 of 88 patients); the between-group difference was not statistically significant ($P = 0.9$). At 12 months, complete remission rates were 48% (35 of 73 patients) and 53% (38 of 72 patients) in the MMF and prednisone groups, respectively; the between-group difference was not statistically significant ($P = 0.6$). Incidences of Cushing syndrome and newly diagnosed diabetes mellitus were lower in the MMF group than in the prednisone group.

Limitations: Not all participants were treated with renin-angiotensin system blockers, relatively short follow-up.

Conclusions: MMF plus prednisone versus full-dose prednisone did not differ in reducing proteinuria, but patients treated with the former had fewer adverse events in patients with IgAN with active proliferative lesions. *Am J Kidney Dis.* ■(■):■-■. © *2017 by the National Kidney Foundation, Inc.*

INDEX WORDS: Mycophenolate mofetil (MMF); prednisone; IgA nephropathy (IgAN); crescents; complete remission; proteinuria; immunosuppression; proliferative lesions; endocapillary hypercellularity; necrosis; biopsy-proven IgAN; renal histology; adverse event; kidney disease; corticosteroid; safety; randomized controlled trial (RCT).

A common glomerular disease, immunoglobulin A nephropathy (IgAN) is an important cause of kidney failure globally. Patients with IgAN have a broad range of clinical presentations, ranging from isolated hematuria to rapidly progressive kidney failure, and also have a variety of histologic lesions, ranging from minimal abnormality on light microscopy to crescentic glomerulonephritis. Currently, which patients need which immunosuppressant and when to introduce the treatment remain challenging questions because no specific disease–targeted treatments exist for IgAN.[1]

The pathogenesis of IgAN, although incompletely understood, is recognized as an autoimmune kidney disease that is a consequence of increased circulating levels of IgA1 with galactose-deficient hinge region

From the [1]National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing; [2]Renal Division, Ruijin Hospital, Shanghai; [3]Renal Division, The First Affiliated Hospital of Zhengzhou University, Zhengzhou; [4]Renal Division, The First Affiliated Hospital of Zhejiang University, Hangzhoua; and [5]Renal Division, West China Hospital, Chengdu, China.

[*] J.-H.H. and W.-B.L. contributed equally to this work.

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Address correspondence to Zhi-Hong Liu, MD, National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, No. 305 Zhongshan East Road, Nanjing 210016, China. E-mail: liuzhihong@nju.edu.cn

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O-glycans and antiglycan autoantibodies.[2] This is one of the rationales for the use of immunosuppression to treat IgAN. However, which kinds of patients with IgAN benefit most from immunotherapy is still unclear, and conflicting results have been reported in the use of immunosuppression to treat IgAN.

The STOP-IgAN (Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgAN) trial, which involved patients with IgAN and persistent proteinuria with protein excretion $>$ 0.75 g/d despite supportive care including blockers of the renin-angiotensin system (RAS) showed no significant effect of adding immunosuppression to continued supportive care, both in terms of change in estimated glomerular filtration rate (eGFR) after 3 years of follow-up or the development of end-stage renal disease (ESRD).[3] However, histologic findings were not taken into consideration in this study, and as such, it is impossible to determine whether its conclusions apply to patients with crescents, endocapillary hypercellularity, and necrosis. Patients with these lesions appear to respond to immunosuppression based on retrospective reviews and observational studies.[4-7] Furthermore, meta-analysis has shown that the presence of any crescents in biopsy samples is associated with kidney failure,[8] suggesting that amelioration of these lesions might benefit kidney outcomes. However, most of these studies lacked either a sufficient sample size or optimal assessment of histologic data to address this issue. Randomized controlled trials (RCTs) are required to support the notion that these lesions have a better response to immunosuppression and can be used to predict treatment response in patients with IgAN.

This multicenter RCT was performed to evaluate the efficacy and safety of mycophenolate mofetil (MMF) plus prednisone compared to full-dose prednisone in patients with IgAN with active proliferative lesions, to elucidate whether these renal histologic lesions have a good response to immunosuppression, and to compare which therapy was superior.

METHODS

Study Design and Participants

This was a prospective, multicenter, randomized, controlled, open-label, 12-month study. Patients were recruited from 5 renal units in China. Inclusion criteria were as follows: (1) biopsy-proven IgAN within 1 month before enrollment; (2) at least 1 of the following histologic lesions: cellular and fibrocellular crescents involving 10% to $<$50% of glomeruli, endocapillary hypercellularity, or glomerular necrosis, with additional inclusion criteria being tubular atrophy/interstitial fibrosis involving $<$50% of the renal pathology; (3) age of 18 to 65 years; and (4) urinary protein excretion $\geq$ 1.0 g/24 h on 2 consecutive measurements within 1 week. We excluded patients with IgAN from a secondary cause and with eGFRs $<$ 30 mL/min/1.73 m^2 (calculated by the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] creatinine equation).[9] Specific details of exclusion and withdrawal criteria are available in Item S1 (provided as online supplementary material).

The study was approved by local ethics committees (approval number 2010NLY-023), and all participants provided written informed consent. The study was performed in accordance with the Declaration of Helsinki and the principles outlined in the "Guidelines for Good Clinical Practice" from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Tripartite Guideline (January 1997).

Randomization

Hangzhou Tigermed Consulting Co Ltd created the randomization list, which was done with a block randomization of 4. Sequentially numbered concealed envelopes containing group assignments were provided to investigators. After eligible patients provided written informed consent, investigators opened the envelopes in sequence, and patients were randomly assigned to the MMF group (MMF plus prednisone) or prednisone group (prednisone only) in a 1:1 ratio.

Procedures

In the MMF group, MMF treatment was initiated at a dosage of 1.5 g/d orally (0.75 g every 12 hours) and was administered for 6 months, while the daily oral prednisone dosage was initiated at 0.4 to 0.6 mg/kg/d taken every morning for 2 months and then tapered by 20% each month for the next 4 months. In the prednisone group, the daily dosage of oral prednisone was initiated at 0.8 to 1.0 mg/kg/d taken every morning for 2 months and then tapered by 20% each month for the next 4 months. In both groups, prednisone treatment was stopped at 6 months. The treatments were then stopped, and patients were followed up for an additional 6 months.

Patient visits were scheduled at months 1, 2, 4, 6, 9, and 12. At 6 months, patients underwent a repeat kidney biopsy if they gave consent. Pathologic features of the baseline and repeat biopsies were independently examined by 2 renal pathologists S.-S.L. and C.-H.Z.) who were masked to the assigned treatment. Kidney biopsies were scored using the Oxford Classification of IgAN (MEST score).[10]

Patients with hypertension (systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg; MMF group, 24.4%; prednisone group, 23.9%) were treated with RAS blockers during the trial. Additional use of calcium channel blockers, β-blockers, and diuretics was allowed. Leflunomide, cyclosporine A, cyclophosphamide, tacrolimus, and methotrexate use was prohibited.

Outcome Measures

The primary end point was the rate of complete remission at both 6 and 12 months, and secondary end points included the rate of overall response (complete remission plus partial remission) at 6 and 12 months, median time to complete remission, relapse rate after stopping the treatments, and changes in active proliferative lesions on a repeat biopsy. Complete remission was defined as proteinuria becoming undetectable, with a stable serum creatinine level (defined as not $>$25% above the baseline). Partial remission was defined as proteinuria with protein excretion $>$ 0.4 to $<$1.0 g/24 h, serum albumin level $\geq$ 35 g/L, and stable serum creatinine level (defined as not $>$25% above baseline). No response was defined as not achieving complete or partial remission criteria. Relapse was defined as remission (complete or partial) followed by proteinuria with protein excretion $>$ 1.0 g/24 h on 2 consecutive measurements. The outcomes were adjudicated by an independent Clinical End Points Committee, blinded to the treatment regimen.

Sample Size and Statistical Analyses

Based on published data, the complete remission rate in the prednisone group was estimated at 20%.[11] Assuming a 25%