Efficacy of Leflunomide, Telmisartan, and Clopidogrel for Immunoglobulin A Nephropathy: A Randomized Controlled Trial

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Abstract

Background: The efficacy and safety of telmisartan combined with clopidogrel, leflunomide, or both drugs for immunoglobulin A nephropathy (IgAN) are unclear. This study was designed to evaluate the efficacy and safety of telmisartan combined with clopidogrel, leflunomide, or both drugs for IgAN.

Methods: It is a multicenter, prospective, double-dummy randomized controlled trial. Primary IgAN patients were recruited in 13 renal units across Beijing, China, from July 2010 to June 2012. After a 4-week telmisartan (80 mg/d) wash-in, 400 patients continuing on 80 mg/d telmisartan were randomly assigned to additionally receive placebo (Group A), 50 mg/d clopidogrel (Group B), 20 mg/d leflunomide (Group C), or 50 mg/d clopidogrel and 20 mg/d leflunomide (Group D). The 24-week intervention was completed by 360 patients. The primary endpoint was change in 24-h proteinuria at 24 weeks. A linear mixed-effect model was used to analyze the changes at 4, 12, and 24 weeks. Generalized estimating equations were used to evaluate changes in hematuria grade. This trial was registered at the Chinese Clinical Trial Registry.

Results: The effects of telmisartan combined with leflunomide on changes in proteinuria (0.36 [95% confidence interval (CI) 0.18–0.55] g/d, $P < 0.001$), in serum uric acid (76.96 [95% CI 57.44–96.49] µmol/L, $P < 0.001$), in serum creatinine (9.49 [95% CI 6.54–12.44] µmol/L, $P < 0.001$), and in estimated glomerular filtration rate (−6.72 [95% CI −9.46 to −3.98] ml·min^{-1}·1.73 m^{-2}, $P < 0.001$) were statistically significant, whereas they were not statistically significant on changes in systolic and diastolic blood pressure and weight ($P > 0.05$). Telmisartan combined with clopidogrel had no statistical effect on any outcome, and there was no interaction between the interventions. No obvious adverse reactions were observed.

Conclusions: Telmisartan combined with leflunomide, not clopidogrel, is safe and effective for decreasing proteinuria in certain IgAN patients.

Trial Registration: chictr.org.cn, ChiCTR-TRC-10000776; http://www.chictr.org.cn/showproj.aspx?proj=8760.

Key words: Clopidogrel; Immunoglobulin A Nephropathy; Leflunomide; Randomized Controlled Trial

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INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most prevalent primary chronic glomerular disease worldwide.[1] In China, IgAN accounts for 33.19% of total renal biopsy diagnoses and 45.26% of primary glomerular diseases.[2] Approximately 10% of IgAN patients demonstrate an accelerated loss of renal function and 30–40% slowly progress to renal failure;[3] however, proteinuria control can improve the prognoses for IgAN.[4] Pathogenesis and progression of IgAN are related to many factors, including heredity, inflammation, renin-angiotensin system activity, extracellular matrix metabolism, and abnormal blood coagulation.[5,6] An effective delay or blockade of IgAN progression may require multiple treatments. Despite a better understanding of the pathogenic mechanisms of IgAN, no targeted treatment is available.

Several classes of drugs have been shown to be efficacious in managing IgAN. Brown et al.[7] reported that prednisolone, azathioprine or cyclophosphamide, dipyridamole, and heparin followed by warfarin improve renal function in patients with rapidly progressive glomerulonephritis. Other studies have found that immunosuppressants combined with antiplatelet/anticoagulant drugs improve renal function in patients with IgAN and other renal diseases.[8-10] These are single-center studies with a small sample size, and results of these studies qualified for a lower level of evidence. Therefore, in a multicenter, prospective, double-dummy randomized clinical trial (RCT), we evaluated the efficacy and safety of the angiotensin receptor blocker (ARB) telmisartan in combination with the antiplatelet drug clopidogrel, the immunosuppressant leflunomide, or both drugs for managing IgAN. The study was implemented before the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines[11] were issued.

METHODS

Patients

Patients were recruited across 13 renal centers in Beijing, China. Inclusion criteria were age 18–55 years, biopsy confirmed (within the past year) IgAN of Lee's grade II–IV, proteinuria of 0.5–3.5 g/d, serum creatinine <265 μmol/L, and blood pressure between 90/60 and 130/80 mmHg with or without antihypertensive treatments. Exclusion criteria were IgAN secondary to other diseases; previous adverse reaction to telmisartan, clopidogrel, or leflunomide; diabetes mellitus; pregnancy or unreliable contraception; and use of corticosteroids or other immunosuppressive agents (including leflunomide) in the preceding 3 months. Patients were recruited through workplace flyers and posters. Individuals who met all eligibility criteria were asked to complete a written informed consent document.

Study design

Participants were recruited from July 2010 to September 2011, and the trial follow-up was completed in June 2012. Patients, providers, and researchers were blinded to treatment allocation. The trial was registered at the Chinese Clinical Trial Registry (No. ChiCTR-TRC-10000776). Ethical approval was obtained from the People's Liberation Army General Hospital Clinical Research Ethics Committee (No. 20100127-002). Each participating center also obtained the local ethical approval. All patients gave written informed consent. There were no changes to the methods after trial commencement. The study was conducted in conformity with the *Declaration of Helsinki*.

Randomization and interventions

Before recruitment, a computer-generated randomization list was produced by a staff member at the Peking University Clinical Research Institute (Beijing, China) who was not otherwise involved in the trial. The randomization sequence was created using SAS statistical software 13.0 (SAS Institute, Cary, NC, USA) with a 1:1:1:1 allocation using a block size of eight, with two participants assigned to each of the four arms. Corresponding supervision measures were taken, and a detailed blind coding was recorded and covertly preserved in the coordinating center. Each study center was randomly stratified according to the enrollment order. Patients who met the eligibility criteria underwent a 4-week wash-in period with 80 mg/d of telmisartan. Baseline data were recorded after the wash-in period. Morphological indices were assessed by light microscopy according to the scoring system of Katafuchi et al.[12] Patients were randomly assigned to Groups A (telmisartan [80 mg/d] + clopidogrel placebo + leflunomide placebo), B (telmisartan [80 mg/d] + clopidogrel [50 mg/d] + leflunomide placebo), and C (telmisartan [80 mg/d] + clopidogrel placebo + leflunomide [20 mg/d]), and 99 were assigned to Group D (telmisartan [80 mg/d] + clopidogrel [50 mg/d] + leflunomide [20 mg/d]). The treatment period was 24 weeks. Leflunomide, clopidogrel, and corresponding placebos were produced by their respective manufacturers in prepacked bottles that were consecutively numbered for each patient according to the randomization schedule. The shape, color, and smell of the placebos were the same as the "true" medicine. The use of conventional antihypertensive drugs, including calcium channel blockers (amlodipine or felodipine), α- and β-receptor antagonists, and thiazide or loop diuretics, was allowed with the aim of achieving a target blood pressure of 130/80 mmHg. The use of steroids, other renin-angiotensin system inhibitors, immunosuppressants, antiplatelet agents, and anticoagulants was excluded during the study period. Patients were followed up to the end of 24-week treatment period.

Outcome measures

The primary outcome was a change in the 24-h urinary protein excretion at 24 weeks. The secondary outcomes included changes in the serum creatinine and estimated glomerular filtration rate (eGFR) as calculated by the chronic kidney disease (CKD) epidemiology collaboration equation which is adjusted for Asian populations,[13] serum uric acid, hematuria, and blood pressure at 24 weeks. These

indices were measured at 4, 12, and 24 weeks. To avoid possible drift among different centers, critical laboratory examinations, such as urine protein and serum creatinine, were all conducted at Chinese People's Liberation Army General Hospital. Urinary protein concentration was measured using the biuret method (Siemens; ADVIA 2400 Biochemical Analyzer, Germany), and 24-h urinary protein excretion was calculated based on concentration and 24-h urine volume. Sarcosine oxidase was used to assay serum creatinine (Roche Cobas 8000 Biochemical Analyzer, Switzerland).

Safety evaluation

Patients whose proteinuria increased to >3.5 g/d, serum creatinine increased to >50% of the previous value or >265 µmol/L, serum potassium exceeded 5.5 mmol/L, or blood pressure dropped below 90/60 mmHg were dropped from the trial. Adverse events such as leukopenia, abnormal liver function, and high potassium were also assessed. Clinicians collected adverse events and assessed severity and potential causality at each visit. The chief investigator categorized the adverse events rated the severity and potential causality of adverse events and decided whether to classify adverse events as open-ended according to the checklist of possible adverse events in the protocol.

Sample size

SAS version 9.2 (GLMPOWER, SAS Institute, Cary, NC, USA) was used to determine the study sample size required to detect changes in urinary protein excretion at 24 weeks with a power of 90% at a significance level of 5%. Based on our previous study, we assumed a mean urinary protein excretion of 1 g/24 h and mean (standard deviation [SD]) decreases in urinary protein excretion of 0.20 ± 0.70, 0.40 ± 0.70, 0.40 ± 0.70, and 0.60 ± 0.70 g/24 h for Group A (telmisartan alone), Group B (telmisartan + clopidogrel), Group C (telmisartan + leflunomide), and Group D (telmisartan + clopidogrel + leflunomide), respectively. Analysis of variance showed that 89 patients per group (total 356 patients) would be required. Allowing for an estimated dropout rate of 10%, we concluded that 400 patients should be recruited.

Statistical analysis

Data were checked manually and double-entered; any obvious error was corrected in the primary records. Categorical variables are presented as number (%) and normally and nonnormally distributed continuous variables as mean (SD) and median (interquartile range), respectively. All patients who completed any of the outcome measures at 4, 12, or 24 weeks were included in the analysis. A linear mixed-effect model with the missing data was used to analyze the changes in proteinuria, serum creatinine, eGFR, serum uric acid, systolic and diastolic blood pressure, and weight at 4,12, and 24 weeks. Generalized estimating equations were used to evaluate changes in hematuria grade. Categorical variables are compared by Chi-square test. Over the 24-week period, compliance, defined as the ratio of the actual amount of medication taken by the patient to the amount provided by the investigator, was assessed at each visit. Good compliance was defined as a ratio ranging from 0.8 to 1.2. Bad compliance was defined as the ratio <0.8 or >1.2. Corresponding 95% confidence interval (*CI*) was calculated. All statistical analyses were performed using SPSS 16.0 software (SPSS, Chicago, IL, USA) and SAS version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

We screened 472 patients between July 2010 and September 2011. After a 4-week wash-in period, 72 patients were excluded from the study and 400 patients were randomly assigned (1:1:1:1) to groups using a random number table. After randomization, one patient was deemed ineligible based on a serum creatinine level of 407 µmol/L after the wash-in period. This patient did not receive the allocated intervention and was not included in the primary analysis. Of the remaining 399 patients, 100 each were assigned to Groups A (telmisartan 80 mg/d + clopidogrel placebo + leflunomide placebo), B (telmisartan 80 mg/d + clopidogrel 50 mg/d + leflunomide placebo), and C (telmisartan80 mg/d + clopidogrel placebo + leflunomide 20 mg/d), and 99 were assigned to Group D (telmisartan 80 mg/d + clopidogrel 50 mg/d + leflunomide 20 mg/d). Ultimately, 360 patients completed the 24-week intervention [Figure 1]. Baseline measurements were similar among the treatment groups [Table 1]. The number of patients receiving concomitant therapy with the calcium channel blockers, α- and β-receptor antagonists, and diuretics was similar among the four groups.

Efficacy analysis

Treatment crossovers did not occur during the trial. Two patients in Groups B and D had bad compliance. Compliance was not statistically different among the four treatment groups. Estimated differences in the changes in proteinuria, serum creatinine, eGFR, serum uric acid, and systolic and diastolic blood pressure between no leflunomide and leflunomide groups (linear mixed-effects model) during the 24-week treatment period are presented in Table 2 and Figure 2. Changes in proteinuria (0.36 [95% *CI* 0.18–0.55] g/d, $F = 8.44$, $P = 0.004$), serum uric acid (76.96 [95% *CI* 57.44–96.49] µmol/L, $F = 61.07$, $P < 0.001$), serum creatinine (9.49 [95% *CI* 6.54–12.44] µmol/L, $F = 32.89$, $P < 0.001$), and eGFR (-6.72 [95% *CI* -9.46 to -3.98] ml·min⁻¹·1.73 m⁻², $F = 23.35$, $P < 0.001$) were statistically different in telmisartan combined with leflunomide, whereas changes in systolic and diastolic blood pressure and weight were not statistically different.

Estimated differences in the changes in proteinuria, serum creatinine, eGFR, serum uric acid, and systolic and diastolic blood pressure between no clopidogrel and clopidogrel groups (linear mixed-effects model) during the 24-week treatment period are presented in Table 3 and Figure 2.
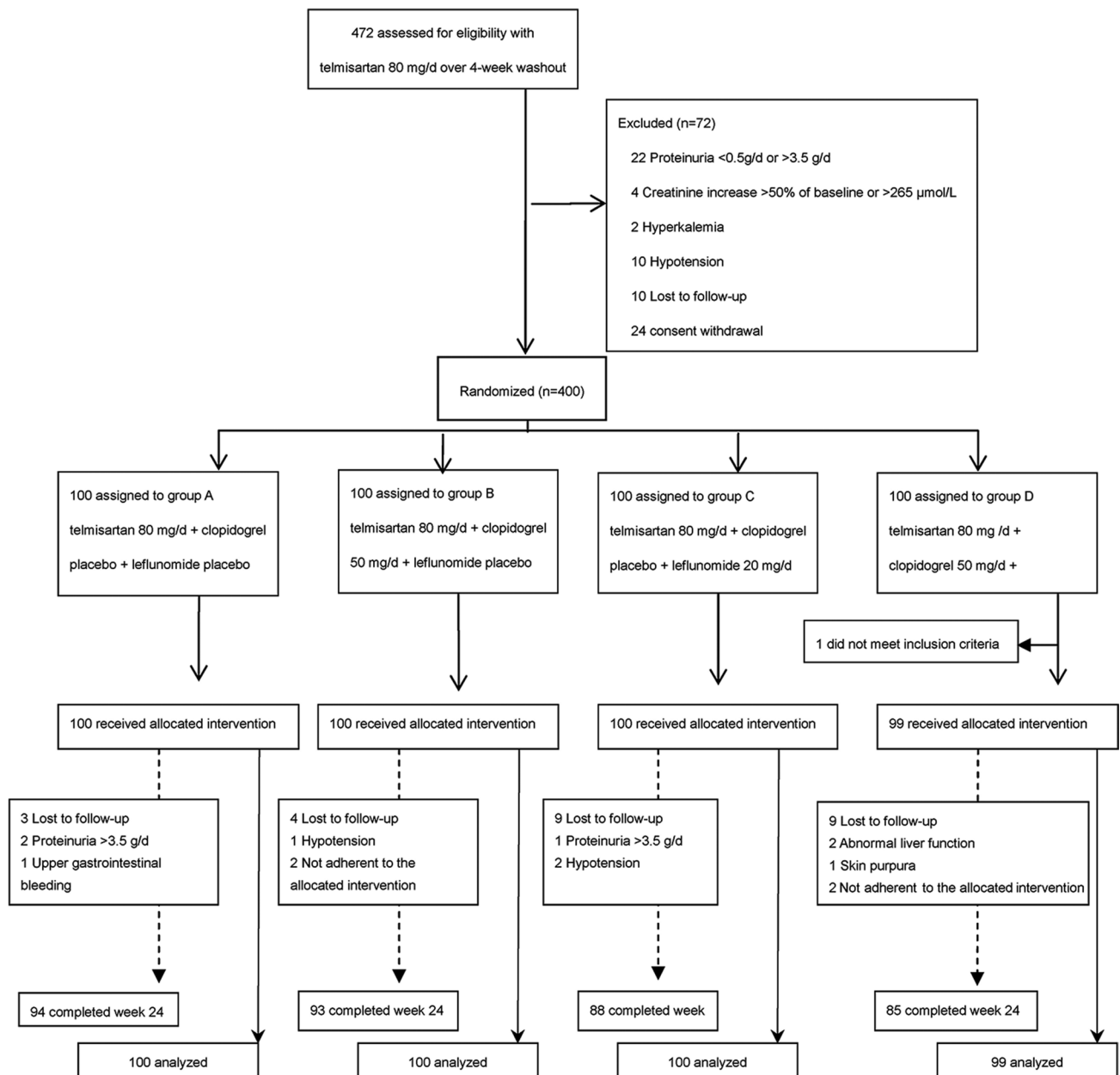
Figure 1: Study flow diagram.

Changes in continuous outcomes were not statistically different in telmisartan combined with clopidogrel. The effects of clopidogrel by leflunomide interaction on changes in continuous outcomes were not clinically relevant. Clopidogrel and leflunomide were not associated with changes in hematuria grade.

Safety analysis

Adverse events according to treatment group are shown in Table 4. Two patients in Group A and one patient in Group C were diagnosed with nephrotic syndrome during routine visits at 30 days, 84 days, and 96 days, respectively. One patient in Group B and two patients in Group C demonstrated hypotension (<90/60 mmHg) at 30 days, 30 days, and 84 days, respectively. Two patients in Group D withdrew from therapy because of abnormal

liver function at 114 and 129 days. One patient in Group A was diagnosed with upper gastrointestinal bleeding 23 days after enrollment. One patient in Group D was diagnosed with skin purpura at 129 days. No serious adverse events occurred.

DISCUSSION

This 24-week RCT of 399 IgAN patients indicates that telmisartan combined with leflunomide is effective for reducing proteinuria, serum creatinine, and uric acid and is effective for increasing eGFR. However, telmisartan combined with clopidogrel turns out to be ineffective.

IgAN is the most common CKD, which has an overall prevalence of 10.8% in China.[14] Effective treatment of IgAN is critical for reducing the incidence of end-stage renal

Table 1: Baseline characteristics of the study population*

Characteristics	Group A[†] (n = 100)	Group B[†] (n = 100)	Group C[†] (n = 100)	Group D[†,‡] (n = 99)	P
Sex (male/female)	54/46	61/39	54/46	62/37	0.466
Age (years)[§]	39.01 (9.78)	36.52 (9.59)	38.12 (10.62)	37.06 (10.46)	0.309
BMI (kg/m²)[§]	24.48 (3.87)	24.06 (3.04)	24.99 (3.48)	24.58 (3.71)	0.331
Weight (kg)[§]	69.27 (13.74)	68.15 (11.27)	70.77 (14.44)	70.16 (13.77)	0.536
Systolic blood pressure (mmHg)[‖]	120.00 (110.00–123.50)	120.00 (110.00–120.00)	120.00 (110.00–124.00)	120.00 (110.00–122.00)	0.637
Diastolic blood pressure (mmHg)[‖]	75.00 (70.00–80.00)	75.50 (70.00–80.00)	78.00 (70.00–80.00)	80.00 (70.00–80.00)	0.615
Proteinuria (g/d)[‖]	1.01 (0.66–1.48)	0.99 (0.68–1.26)	1.04 (0.63–1.50)	1.05 (0.69–1.52)	0.974
Hematuria					
0/1+/2+/3+	13/48/26/13	19/38/32/11	18/36/25/21	15/49/29/6	0.097
Serum creatinine (μmol/L)[§]	88.18 (34.34)	89.03 (29.32)	90.37 (28.44)	96.61 (37.95)	0.258
Serum uric acid (μmol/L)[§]	361.49 (92.09)	367.64 (92.00)	387.46 (100.09)	385.53 (99.23)	0.151
Albumin (g/L)[§]	43.56 (3.77)	44.17 (3.20)	44.61 (4.01)	44.22 (3.64)	0.253
Blood potassium (mmol/L)[§]	4.30 (0.40)	4.38 (0.40)	4.31 (0.38)	4.28 (0.42)	0.325
eGFR-EPI (ml·min⁻¹·1.73 m⁻²)[§]	95.16 (29.02)	96.03 (28.00)	92.06 (26.39)	91.87 (31.33)	0.650
Morphologic indices (n)[¶]					
Glomerular lesions[§]	4.27 (1.71)	4.54 (1.78)	4.74 (1.75)	4.78 (1.57)	0.155
Tubulointerstitial lesions[§]	3.57 (1.91)	3.49 (1.74)	3.65 (1.76)	3.56 (1.77)	0.957
Arterial lesions[§]	1.32 (1.64)	1.17 (1.77)	0.94 (1.12)	1.06 (1.56)	0.433
Sum[§]	9.06 (4.10)	9.39 (3.96)	9.61 (3.59)	9.61 (3.90)	0.827

*Baseline characteristics were measured at the start of the study treatment in each group after a 4-week wash-in period; [†]Group A: Telmisartan 80 mg/d + placebo, Group B: Telmisartan 80 mg/d + 50 mg/d clopidogrel, Group C: Telmisartan 80 mg/d + 20 mg/d leflunomide, Group D: Telmisartan 80 mg/d + 50 mg/d clopidogrel + 20 mg/d leflunomide; [‡]One patient did not receive the allocated intervention and was not included in the primary analysis; [§]Normally distributed continuous variables are presented as mean (SD); [‖]Nonnormally distributed continuous variables are presented as median (IQR); [¶]Morphologic indices of patients in the present study were assessed by light microscopy according to the scoring system of Katafuchi *et al*. BMI: Body mass index; eGFR-EPI: Estimated glomerular filtration rate as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation adjusted for Asian populations; IQR: Interquartile range; SD: Standard deviation.

disease in China.[15] Many studies have identified severe proteinuria as a risk factor associated with deterioration to end-stage renal disease.[16-19]

Although many clinical studies have shown that angiotensin-converting enzyme inhibitor/angiotensin II type 1 receptor blockers (ACEI/ARBs) therapy can effectively reduce the proteinuria and protect renal function in IgAN patients, many individuals with clinical proteinuria cannot achieve effective control with ACEI/ARB therapy alone, and some patients with hypotension cannot be tolerated ACEI/ARB therapy. KDIGO suggests the use of corticosteroid therapy in patients who are unable to achieve a proteinuria reduction of <1.0 g/d after 3–6 months of ACEI/ARB treatment. The use of immunosuppressive agents for IgAN treatment remains controversial based on English-language MEDLINE search (until May 2016). A multicenter RCT of 207 IgAN patients in Italy and Switzerland found no statistical difference between prednisone and prednisone plus low-dose azathioprine in decreasing the proteinuria or improving renal function.[20] A new study also showed that the addition of immunosuppressive therapy to intensive supportive care in patients with high-risk IgAN did not significantly improve the full clinical remission, and during the 3-year study phase, more adverse effects were observed among the patients who received immunosuppressive therapy, with no change in the rate of decrease in the eGFR.[21] Conversely, a small-sample British RCT reported

that low-dose cyclophosphamide followed by azathioprine was associated with a much higher survival (72%) compared with the control treatment (6%).[22] Both of the two Chinese RCT found that cyclosporine A in combination with prednisone remarkably reduced the levels of proteinuria and ameliorated the renal function in the IgAN.[23,24] A Japanese RCT found that the rate of proteinuria disappearance in IgAN patients receiving a combination of prednisone, azathioprine, warfarin, and dipyridamole (92%) was much better than that in patients receiving only hormone therapy (74%).[25] Previous investigations have revealed that mycophenolate mofetil effectively decreases proteinuria in IgAN patients;[26,27] however, another study reported no such effect.[28] The study findings are currently too heterogeneous to support the use of mycophenolate mofetil for IgAN.[29] Leflunomide is effective for treating systemic lupus erythematosus and lupus nephritis.[30,31] Its effectiveness in the treatment of nephrotic syndrome[32] and IgAN[33,34] has also been reported with small samples. Our findings confirm the reported effectiveness of leflunomide in reducing the proteinuria in IgAN patients. Proteinuria reduction is not a goal by itself but a surrogate endpoint for placing the disease in remission or slowing the progression to end-stage renal disease. The immunomodulating effects of leflunomide may be related to its selective inhibition of *de novo* pyrimidine synthesis. Leflunomide inhibits dihydroorotate dehydrogenase and thereby blocks the *de novo* pathway of pyrimidine nucleotide synthesis,
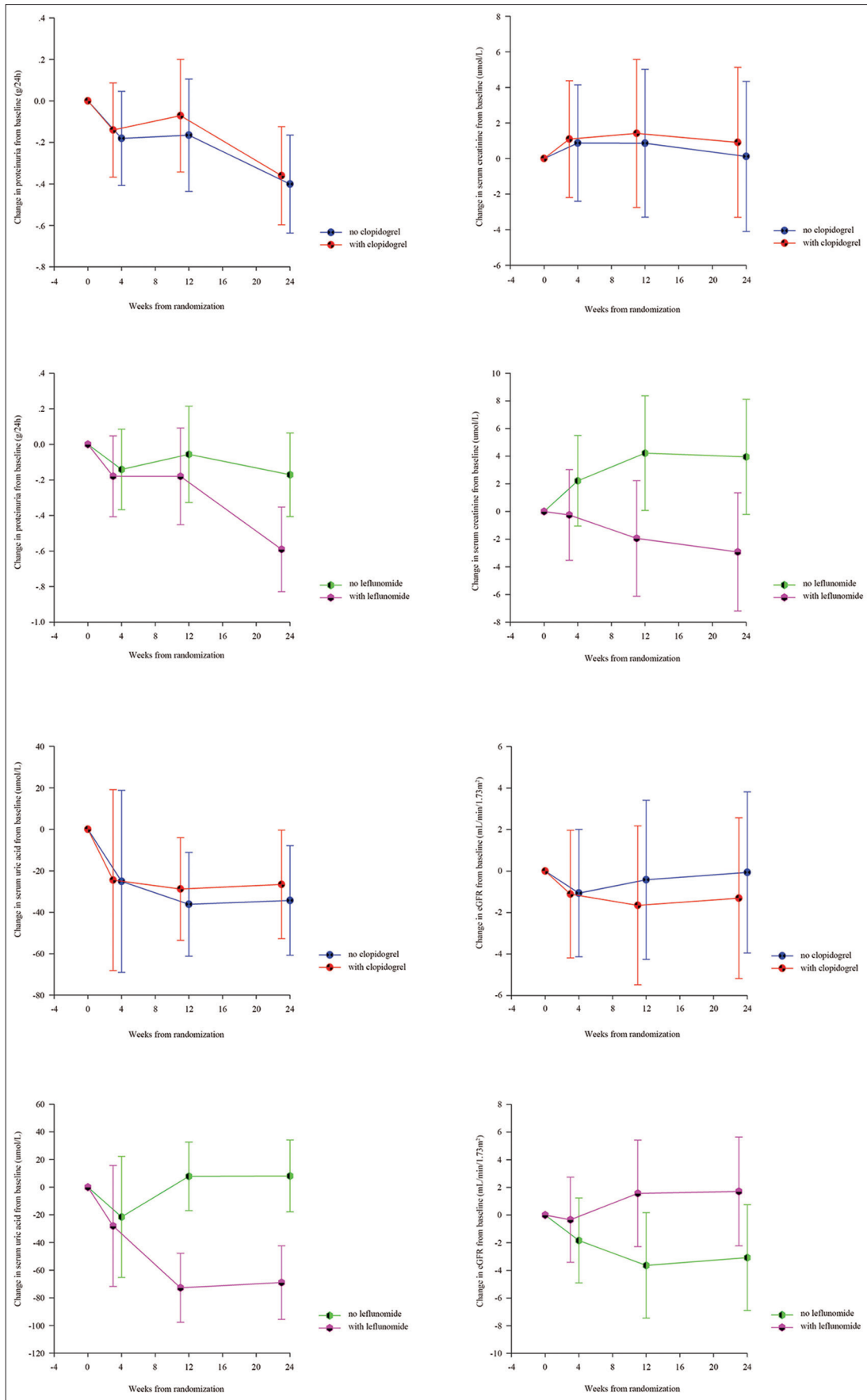
Figure 2: Estimated mean change curves for proteinuria, serum uric acid, serum creatinine, and estimated glomerular filtration rate according to treatment group (linear mixed-effect model). Error bars represent 95% confidence intervals.

Table 2: Estimated differences in the changes in proteinuria, serum creatinine, estimated glomerular filtration rate, serum uric acid, and systolic and diastolic blood pressure between no leflunomide and leflunomide groups during the 24-week treatment period (linear mixed-effects model)

Characteristic	No leflunomide			Leflunomide			Differences			
	n	Mean	95% *CI*	*n*	Mean	95% *CI*	Mean	95% *CI*	*F*	*P*
Changes in proteinuria from baseline (g/24 h) (weeks)										
4	200	−0.14	−0.23 to −0.05	199	−0.18	−0.27 to −0.09	0.36	0.18 to 0.55	8.44	0.004
12	197	−0.06	−0.17 to 0.05	193	−0.18	−0.29 to −0.07				
24	189	−0.17	−0.27 to −0.08	176	−0.59	−0.69 to −0.49				
Changes in serum creatinine from baseline (μmol/L) (weeks)										
4	200	2.22	0.90 to 3.54	199	−0.25	−1.57 to 1.07	9.49	6.54 to 12.44	32.89	<0.001
12	197	4.19	2.52 to 5.86	193	−1.95	−3.63 to −0.26				
24	189	4.30	2.62 to 5.98	176	−2.90	−4.62 to −1.17				
Changes in eGFR from baseline (ml·min⁻¹·1.73 m⁻²) (weeks)										
4	200	−1.83	−3.07 to −0.60	199	−0.34	−1.58 to 0.90	−6.72	−9.46 to −3.98	23.35	<0.001
12	197	−3.64	−5.18 to −2.10	193	1.57	0.01 to 3.12				
24	189	−3.47	−5.04 to −1.90	176	1.90	0.29 to 3.52				
Changes in serum uric acid from baseline (μmol/L) (weeks)										
4	197	−21.41	−39.05 to −3.77	197	−28.01	−45.65 to −10.38	76.96	57.44 to 96.49	61.07	<0.001
12	194	7.85	−2.15 to 17.85	191	−72.75	−82.82 to −62.67				
24	186	8.12	−2.38 to 18.61	175	−68.96	−79.68 to −58.24				
Changes in systolic blood pressure from baseline (mmHg) (weeks)										
4	200	0.44	−0.63 to 1.52	199	−0.84	−1.92 to 0.24	−0.07	−2.99 to 2.86	0.84	0.361
12	196	−0.17	−1.47 to 1.12	189	−0.53	−1.84 to 0.79				
24	186	0.17	−1.28 to 1.62	171	−0.30	−1.79 to 1.19				
Changes in diastolic blood pressure from baseline (mmHg) (weeks)										
4	200	−0.78	−1.61 to 0.05	199	−0.14	−0.97 to 0.69	−0.30	−2.34 to 1.74	0.48	0.489
12	196	−1.15	−2.13 to −0.18	189	−0.42	−1.41 to 0.56				
24	186	−0.24	−1.25 to 0.77	171	−0.46	−1.50 to 0.58				

CI: Confidence interval; eGFR: Estimated glomerular filtration rate.

which is crucial for T-cell activation and proliferation. Leflunomide is also an inhibitor of protein tyrosine kinases which play a fundamental role in the intracellular signal transduction triggered by cytokines.[35] These immunomodulatory properties may confer a beneficial effect against IgAN because inflammation and circulating immune complexes play an important role in the onset and progression of IgAN. At low therapeutically applicable doses, the active metabolite of leflunomide (A771726) reversibly inhibits dihydroorotate dehydrogenase, which is the rate-limiting enzyme in *de novo* pyrimidine synthesis. Evidence suggests that the observed anti-inflammatory effects of A771726 may be related to its ability to suppress interleukin-1, and the tumor necrosis factor downregulates the glycosylation of adhesion molecules while reducing the T lymphocyte/monocyte contact activation during inflammation.[36] We also found that the serum creatinine and uric acid levels statistically decreased in IgAN patients taking leflunomide, whereas the eGFR was statistically

increased. A previous study also showed that leflunomide reduced the uric acid levels in rheumatoid arthritis patients.[37] A meta-analysis demonstrated a positive association between the serum uric acid levels and risk of CKD.[38] Furthermore, uric acid-lowering therapy with allopurinol may hinder CKD progression.[39] Therefore, the leflunomide-associated reduction in uric acid may have contributed to the improvements in IgAN in our study.

Blood coagulation and platelet activation are also involved in IgAN progression.[40] Some RCTs have demonstrated that anticoagulant/antiplatelet therapy reduces urinary protein in IgAN patients.[40-42] We found that the ARB irbesartan combined with clopidogrel had renal protective effects in CKD animal models.[11] In the present study, clopidogrel did not reduce the proteinuria or protect renal function in IgAN patients.

This study has some limitations. First, a 24-week randomized controlled study is not sufficient for evaluating the long-term

Table 3: Estimated differences in the changes in proteinuria, serum creatinine, estimated glomerular filtration rate, serum uric acid, and systolic and diastolic blood pressure between no clopidogrel and clopidogrel groups during the 24-week treatment period (linear mixed-effects model)

Characteristic	No clopidogrel			Clopidogrel			Differences			
	n	Mean	95% *CI*	*n*	Mean	95% *CI*	Mean	95% *CI*	*F*	*P*
Changes in proteinuria from baseline (g/24 h) (weeks)										
4	200	−0.18	−0.27 to −0.09	199	−0.14	−0.23 to −0.05	−0.07	−0.26 to 0.12	0.77	0.380
12	195	−0.17	−0.27 to −0.06	195	−0.07	−0.18 to 0.04				
24	182	−0.40	−0.50 to −0.31	183	−0.36	−0.46 to −0.26				
Changes in serum creatinine from baseline (μmol/L) (weeks)										
4	200	0.87	−0.45 to 2.19	199	1.09	−0.23 to 2.42	3.09	−0.35 to 6.53	0.13	0.716
12	195	0.85	−0.82 to 2.53	195	1.39	−0.29 to 3.07				
24	182	0.58	−1.13 to 2.28	183	0.83	−0.88 to 2.53				
Changes in eGFR from baseline (ml·min⁻¹·1.73 m⁻²) (weeks)										
4	200	−1.06	−2.30 to 0.18	199	−1.11	−2.35 to 0.13	−1.19	−4.42 to 2.03	0.81	0.368
12	195	−0.41	−1.96 to 1.13	195	−1.65	−3.20 to −0.11				
24	182	−0.30	−1.90 to 1.29	183	−1.27	−2.86 to 0.33				
Changes in serum uric acid from baseline (μmol/L) (weeks)										
4	196	−24.99	−42.67 to −7.30	198	−24.44	−42.03 to −6.85	−5.99	−27.33 to 15.36	0.54	0.461
12	191	−36.11	−46.20 to −26.03	194	−28.78	−38.78 to −18.79				
24	178	−34.24	−44.90 to −23.57	183	−26.61	−37.15 to −16.07				
Changes in systolic blood pressure from baseline (mmHg) (weeks)										
4	200	−0.21	−1.28 to 0.87	199	−0.19	−1.27 to 0.89	−0.88	−3.85 to 2.09	0.05	0.829
12	193	−0.42	−1.72 to 0.88	192	−0.28	−1.58 to 1.02				
24	177	−0.24	−1.71 to 1.23	180	0.11	−1.36 to 1.57				
Changes in diastolic blood pressure from baseline (mmHg) (weeks)										
4	200	−0.19	−1.02 to 0.64	199	−0.73	−1.56 to 0.10	1.07	−1.00 to 3.15	2.93	0.090
12	193	−0.44	−1.41 to 0.54	192	−1.14	−2.13 to −0.16				
24	177	0.45	−0.58 to 1.47	180	−1.14	−2.17 to −0.12				

CI: Confidence interval; eGFR: Estimated glomerular filtration rate.

Table 4: Adverse events according to each treatment group, *n*

Adverse events	Group A* (n = 100)	Group B* (n = 100)	Group C* (n = 100)	Group D*,† (n = 99)	P
Death	0	0	0	0	1.000
Patient withdrew due to adverse events	1	1	2	3	0.663
Any adverse event	4	7	4	9	0.353
Any serious adverse event‡	0	0	0	0	1.000
Abnormal liver function	0	3	1	3	0.267
Hypotension	0	1	2	0	0.298
Hyperkalemia	1	2	1	0	0.571
Neutropenia	1	0	0	2	0.292
Rash	0	0	0	2	0.107
Skin purpura	0	0	0	1	0.386
Upper gastrointestinal bleeding	0	0	0	1	0.386
Herpes zoster	1	0	0	0	0.392
Urinary tract infection	0	1	0	0	0.392
Upper respiratory tract infection	1	0	0	0	0.392

*Group A: Telmisartan 80 mg/d + placebo, Group B: Telmisartan 80 mg/d + 50 mg/d clopidogrel, Group C: Telmisartan 80 mg/d + 20 mg/d leflunomide, Group D: Telmisartan 80 mg/d + 50 mg/d clopidogrel + 20 mg/d leflunomide; †One patient did not receive the allocated intervention and was not included in the primary analysis; ‡Severe adverse events refer to adverse events that cause initial or prolonged hospitalization, handicaps, employment handicaps, congenital malformation, life-threatening health events, or death.

efficacy of leflunomide for managing IgAN. Second, since this study began before the KDIGO 2012 guidelines were issued, our treatment protocol conflicted with these guidelines. The KDIGO guidelines do not support the use of antiplatelet or immunosuppressive agents, except in cases of crescentic IgAN with rapid deterioration. Third, a wash-in period of 4 weeks was too short and a fixed dose of telmisartan was used rather than up-titration dosage. Lastly, considering the reported discrepancies in the effects of immunosuppressive agents (specifically mycophenolate mofetil) between Chinese and European IgAN patients, our study findings only apply to Chinese patients until they can be confirmed in subjects of other ancestries.

In conclusion, this multicenter, prospective, double-dummy RCT confirms the efficacy and safety of telmisartan combined with leflunomide in reducing proteinuria of IgAN patients. However, telmisartan combined with clopidogrel turns out to be ineffective. This results may provide an option for IgAN patients in whom telmisartan alone is insufficient for lowering proteinuria. However, the long-term efficacy and safety of telmisartan combined with leflunomide in IgAN patients remain to be determined.

Conflicts of interest
There are no conflicts of interest.

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