Efficacy and Safety of Telmisartan, Clopidogrelin, and Leflunomide in patients with IgA nephropathy - a multicentre, prospective, randomized, double-blind and -dummy controlled clinical trial

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Objective

To evaluate the efficacy and safety of telmisartan combined with clopidogrelin and/or leflunomide for patients with IgA nephropathy and whether the combination therapy surpass telmisartan in decreasing proteinuria and protecting renal function.

Methods

We enrolled 400 patients aged 18-55 years from 13 centers in Beijing who had proteinuria 0.5~3.5g per day, baseline serum creatinine (SCr) <265.2μmol/L (3mg/dl). All patients were eluted by taking telmisartan 80mg per day for 4 weeks and then randomly assigned to receive at least 24 weeks of treatment with telmisartan 80mg per day + clopidogrelin placebo + leflunomide placebo (group A), telmisartan 80mg per day + clopidogrelin 50mg per day + leflunomide placebo (group B), telmisartan 80mg per day + clopidogrelin placebo + leflunomide 20mg per day (group C), telmisartan 80mg per day + clopidogrelin 50mg per day + leflunomide 20mg per day (group D). Comparison of 24-hr urinary protein excretion, the serum creatinine, eGFR, albumin, cholesterol and uric acid, before and after the therapy were assessed.

Results

- No statistically significant differences were observed for any baseline clinical data including age, gender , BMI , blood pressure , proteinuria, serum creatinine, eGFR, serum uric acid in the four groups (P>0.05). (table1)
- After treatment for 24 weeks, a significant decline of proteinuria was observed in the four groups (P <0.05), while those in group C (1.20±0.76 vs 0.77±0.42 g/24h) and group D (1.16±0.63 vs 0.74±0.49 g/24h) were decreased more significantly than in group A (1.15±0.87 vs 0.92±0.58 g/24h) and group B (1.11±0.83 vs 0.89±0.42 g/24h) (P<0.05). Mixed effects were showed that telmisartan, leflunomide, and telmisartan combined with leflunomide were effective in lowering proteinuria (P<0.01) by model analysis. (table2、3)
- The extent of serum creatinine decline in group C and group D displayed more significantly than that in group A and group B (P<0.05) (table4). The levels of eGFR in group C and group D were increased more than those in group A and group B (table5).
- The decline of serum uric acid in group C and group D displayed more significantly than group A and group B (P<0.05).
- There were no significant differences in the results of albumin and cholesterol among the four groups (P > 0.05).
- No obvious adverse reactions were found in the four groups.

table 1 Comparison of baseline clinical characteristics in patients with IgA nephropathy

	A N=100	B N=100	C N=100	D N=100	*P*
sex (M/F)	54/46	61/39	54/46	63/37	0.439
age	39.01± 9.78	36.52± 9.59	38.12± 10.62	36.93± 10.48	0.225
BMI(kg/m^2)	24.48± 3.87	24.06± 3.04	24.99± 3.48	24.58± 3.69	0.350
Systolic blood pressure mmHg	116.00± 10.22	116.93± 12.22	117.30± 10.64	117.76± 10.04	0.633
Diastolic blood pressure mmHg	74.52± 7.70	74.89± 7.19	74.49± 8.01	75.46± 6.89	0.637
Proteinuria g/day	1.15± 0.87	1.11± 0.83	1.20± 0.76	1.16± 0.63	0.154
Serum creatinine umol/L	88.18±34.34	89.03±29.32	90.37±28.44	97.88±39.82	0.329
Serum urea umol/L	361.49±92.09	367.64±92.00	387.46±100.60	385.37±98.73	0.206
Serum albumin g/L	43.97± 5.77	44.17± 3.20	44.61± 4.01	44.16± 3.66	0.249
eGFR- MDRD (ml/min/1.73m^2)	89.46±32.08	89.90±31.19	84.40±26.54	84.24±31.60	0.249
eGFR-EPI (ml/min/1.73m^2)	95.16±29.02	96.03±28.00	92.06±26.39	91.31± 31.67	0.651

table2 Comparison of Proteinuria from baseline to 24 weeks of therapy

Proteinuria g/d	A N=100	B N=100	C N=100	D N=100	*P* (between groups)
baseline	1.15± 0.87	1.11± 0.83	1.20± 0.76	1.16± 0.63	0.154
24weeks	0.92± 0.58*	0.89± 0.42*	0.77± 0.42**	0.74± 0.49**	< 0. 05
descender	0.22±2.68	0.21±0.77	0.43±0.64△▲	0.42±0.67△▲	< 0. 05

★ compared with basiline in each group, *P*<0.05;
★compared proteinuia with group A at 24 weeks, *P*<0.05;☆ compared proteinuia with group B at 24 weeks, *P*<0.05; △compared proteinuia descender with group A at 24 weeks, *P*<0.05;▲ compared proteinuia descender with group B at 24 weeks, *P*<0.05

table3 analysis of variance for Proteinuria

factor / effect	statistic F	*P*
time	44.88	<.0001
clopidogrelin	0	0.997
leflunomide	0.81	0.009
time*clopidogrelin	0.65	0.583
time*leflunomide	11.84	<.0001
clopidogrelin*leflunomide	0.05	0.824
time*clopidogrelin*leflunomide	1.94	0.123

table4 Comparison of Serum creatinine from baseline to 24 weeks of therapy

Serum creatinine (umol/L)	A N=100	B N=100	C N=100	D N=100	*P* (between groups)
baseline	88.18± 34.34	89.03± 29.32	90.37± 28.44	97.88± 39.82	0.329
24weeks	88.97± 34.95	94.82± 33.03	89.24± 29.57	99.63± 73.08	>0.05
descender	-1.21± 8.78	-3.43± 8.59	-1.20± 10.85△▲	0.57± 11.11△▲	<0.05

△compared serum creatinine descender with group A at 24 weeks, *P*<0.05;
▲ compared serum creatinine descender with group B at 24 weeks, *P*<0.05

Table5 Comparison of eGFR from baseline to 24 weeks of therapy

eGFR (ml/min/1.73m^2)	A N=100	B N=100	C N=100	D N=100	*P* (between groups)
MDRD					
baseline	89.46± 32.08	89.90± 31.19	84.40± 26.54	84.24± 31.60	>0.05
24weeks	88.00± 29.06	84.43± 30.01	86.33± 27.83	87.02± 33.72	>0.05
increased	-1.63± 15.06	-5.46± 12.72	1.93± 14.20 ▲▲▲▲	2.78± 13.62 ▲▲▲▲	<0.01
EPI					
baseline	95.16± 29.02	96.03± 28.00	92.06± 26.39	91.31± 31.67	>0.05
24weeks	94.99± 27.92	91.34± 29.08	93.95± 26.89	93.59± 32.25	>0.05
increased	-0.36± 12.00	-4.69± 11.47	1.89± 12.52 ▲▲ ▲▲	2.28± 10.89 ▲▲▲▲	<0.01

▲▲ compared eGFR increased with group A at 24 weeks,*P*<0.01
▲▲ compared eGFR increased with group B at 24 weeks,*P*<0.01

Conclusion

In the selected patients with IgA nephropathy, telmisartan combined with leflunomide was safe and effective in decreasing proteinura and protecting short-term renal function. Larger randomized studies would be needed to confirm these results in the long run.

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