Int J Clin Exp Med 2020;13(10):7286-7294
www.ijcem.com /ISSN:1940-5901/IJCEM0112729

Review Article

The effects of benazepril combined with losartan potassium on the immune function and inflammatory response in chronic glomerulonephritis patients

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Received April 17, 2020; Accepted August 9, 2020; Epub October 15, 2020; Published October 30, 2020

Abstract: This study aims to investigate the effects of benazepril combined with losartan potassium on the immune function and inflammatory response in patients with chronic glomerulonephritis (CGN). Forty-eight CGN patients who received benazepril treatment from March 2018 to February 2019 were enrolled in the monotherapy group (MG). Meanwhile, another 48 patients who received benazepril + losartan potassium treatment were included in the combination therapy group (CTG). Their IgA, IgG, CD4+, CD8+, CD4+/CD8+, IL-1, IL-6, TNF-α, Scr, BUN, and 24 h urine protein levels were measured. The correlations of the IL-1, IL-6, and TNF-α levels with clinical efficacy were analyzed using Spearman tests. After the treatment, the IgA, IgG, CD4+, and CD4+/CD8+ levels in the CTG were notably higher than they were in the MG ($P<0.01$), but the CD8+ levels were notably lower than they were in the MG ($P<0.001$). The IgA level in the MG was not significantly different from its pre-treatment level ($P>0.05$). After the treatment, the IL-1, IL-6, TNF-α, SCr, BUN, and 24 h urine protein levels in the CTG were remarkably lower than they were in the MG ($P<0.001$). A Spearman analysis revealed that the clinical efficacy gradually improved with the decrease in the IL-1, IL-6, and TNF-α levels. In conclusion, benazepril combined with losartan potassium can significantly improve the immune function, inflammatory response, and renal function of CGN patients.

Keywords: Chronic glomerulonephritis, benazepril, losartan potassium, immune function, inflammatory reaction

Introduction

Chronic kidney disease is related to increased mortality, increased health care expenditures, and decreased quality of life, and chronic glomerulonephritis (CGN) is an important cause of exacerbating the progress of chronic kidney disease [1]. Research shows that CGN patients account for about 21.4% of patients with chronic kidney disease [2]. The glomerular filtration rate (GFR) is a measure of overall renal function, and it has become a significant clinical tool in the daily care of patients with CGN [3]. CGN can lead to severe renal failure, and patients with severe proteinuria, severe hypertension, and significantly elevated creatinine levels have a poor prognosis [4]. Therefore, getting effective treatment is the key to treating this condition.

Hypertension is a common clinical symptom of chronic kidney disease, and almost all patients will suffer from it when GFR decreases. Drug therapy is the main treatment for CGN at present [5]. Angiotensin II receptor antagonists (ARB) and angiotensin converting enzyme inhibitors (ACEI) have protective effects on CGN patients' kidneys, and they can improve patients' quality of life and the therapeutic effect [6]. Benazepril is an ACEI drug which has been approved by the FDA to treat hypertension, either alone or in combination with other antihypertensive drugs [7]. As a hormone that regulates blood pressure, angiotensin II (Ang II) is produced by the renin-angiotensin system (RAS). ACEI drugs can block the production of Ang II, leading to a reduction in systemic arterial blood pressure and an increase in urinary Na+ excretions. It is used to treat hypertension in patients with renal dysfunction [8, 9]. ARB drugs have been found to have a great effect on reducing blood pressure in patients with chronic kidney disease [10], and ACEI and ARB can reduce proteinuria and protect the kidneys

[11]. Unlike ACEI's mechanism of action, ARB antagonizes the Ang II receptor AT 1 without blocking the Ang II formation pathway [12]. Losartan potassium is an ARB drug. Currently, there is little research on CGN in clinical treatment with benazepril combined with losartan potassium. Therefore, this combination therapy will be used to treat CGN patients in this research to study the effects of the combination therapy on patients' immune function, inflammatory response, and renal function, so as to provide a more effective treatment method reference for the clinical treatment of CGN.

Materials and methods

Patient clinical data

A total 96 CGN patients diagnosed and treated at the Xian Ninth Hospital from March 2018 to February 2019 were recruited as the study cohort. Among them, 48 were placed in the monotherapy group (MG) and received benazepril treatment, and the other 48 were placed in the combination therapy group (CTG) and received benazepril + losartan potassium treatment. This study was performed with the approval of the medical ethics committee of Xian Ninth Hospital and was carried out in accordance with Helsinki Declaration. All the participants and their families signed informed consent forms before the study began.

Inclusion and exclusion criteria

Inclusion criteria: Patients who met the CGN diagnostic criteria [13], patients who cooperated with the treatment, patients who had complete clinical data, and patients who met the indications of benazepril and losartan potassium.

Exclusion criteria: Patients who were pregnant or lactating, patients with a history of renal transplantation, patients also suffering from bilateral renal artery stenosis or renal hypofunction, anuria, and patients with a sulfonamide allergy, other kidney diseases, mental disorders, or malignant tumors.

Therapies

Benazepril (Beijing Novartis Pharmaceutical Co., Ltd., SFDA approval number: H2000514) was given orally once/d and 10 mg/time in the MG. Benazepril combined with losartan potassium (Sichuan Hairong Pharmaceutical Co., Ltd., Yangzijiang Pharmaceutical Group, SFDA approval number: H20080371) was given orally once/d and 50 mg/time in the CTG. Both groups of patients were treated continuously for 3 months.

Sample collection and detection

Before and after the treatment, 5 ml of blood was taken from a vein on an empty stomach, left at room temperature for 30 minutes, and centrifuged for 10 minutes at 3000 g at 4°C. The supernatant was absorbed and put in a freezer at -80°C.

The serum IgA and IgG levels were measured using a fully automatic coagulometer (Beckman Coulter, USA, ACL7000), and the CD4+, CD8+, CD4+/CD8+ levels were determined using flow cytometry (FCM, ACEA Biosciences, USA, CytoFLEX).

The IL-1, IL-6 and TNF-α levels were measure using ELISA kits (the kits were IL1F9 ELISA kits, Kemin Mall, article number: SEL621Hu-1, human interleukin-6 (IL-6) ELISA Kit, Shanghai Xinfan Biotechnology Co., Ltd., article number XFH10605, human tumor necrosis factor α (TNF-α) ELISA KIT, Shanghai Xinfan Biotechnology Co., Ltd., article number XF-HUMAN-1766, respectively). Gal-3 antibody was was pre-coated onto a 96-well microplate, then mixed with a standard substance and a detection sample. Then, biotinylated Gal-3 was added and fully washed to remove the unbound biotinylated antibody. HRP-labeled avidin was then added, and a TMB substrate was added for color development after it was washed again. The TMB turned blue under catalysis and yellow under the action of acid. The absorbance (OD value) was measured at the 450 nm wavelength with the help of a microplate reader, and the corresponding concentration was converted based on a standard curve.

Outcome measures

The main outcome measures: the changes in the immune function indexes (IgA, IgG, CD4+, CD8+, CD4+/CD8+) and the inflammatory factors (IL-1, IL-6, TNF-α) before and after the treatment were observed.

The secondary outcome measures: the changes in the patients' renal function indexes in the

Table 1. Evaluation criteria for the clinical efficacy

Clinical efficacy	Evaluation criteria for the clinical efficacy
Recovered	Clinical symptoms disappeared, 24 h urine protein returned to the normal level, and renal function returned to normal.
Markedly effective	Clinical symptoms disappeared significantly, renal function improved significantly, and 24 h urinary protein level decreased by >40% compared with that before treatment.
Effective	The clinical symptoms were improved to a certain extent, and the 24 h urine protein level was reduced by 20%-40% compared with the pre-treatment level.
Ineffective	There were no changes or deterioration in clinical symptoms or the 24 h urine protein quantification.

two groups before and after the treatment were observed. The renal function indexes included serum creatinine (SCr), blood urea nitrogen (BUN), and 24-hour urine protein (24 h urine protein). The treatment effectiveness rates of the two groups were observed, and the correlations between the inflammatory factor levels and clinical efficacy were observed. The evaluation criteria of the clinical efficacy are shown in **Table 1**.

Statistical analysis

SPSS 20.0 (Cabit Information Technology Co., Ltd., Shanghai, China) was applied for the statistical analysis of the collected data. The figures were created using Prism 7 (SOFTHEAD Inc., Shenzhen, China). The enumeration data were represented as (%), and the comparisons were qualified using chi-square tests, represented by χ^2. The (means ± SD) were applied to represent the measurement data. Independent sample t tests were used for the comparisons of normally distributed data between the two groups. Paired t tests were adopted for the comparisons between the two groups before and after treatment, represented by t. The correlation between the expressions of the inflammatory factors in the patients' serum and clinical efficacy were tested using Spearman's test. P<0.05 indicated a significant difference between the two groups.

Results

A comparison of the two groups' general clinical data

A comparison of the general clinical data between the CTG and the MG revealed that there were no significant differences in terms of gender, age, body mass index (BMI), course of the disease, pathological type, educational level, residence, smoking history, or drinking history between the two groups, which were comparable (P>0.05) **Table 2**.

A comparison of the two groups' immune function indexes

By determining the levels of the immune indexes before and after the treatment in the two groups, it was found that there were no significant differences in the IgA, IgG, CD4+, CD8+, and CD4+/CD8+ levels between the two groups before the treatment. After the treatment, the IgA, IgG, CD4+, and CD4+/CD8+ levels in the CTG were notably higher than they were in the MG, and the CD8+ level was notably lower than it was in the MG, as shown in **Figure 1**.

A comparison of the inflammatory factor levels in the two groups

By measuring the inflammatory factor levels before and after the treatment, it was found that there was no significant differences in the IL-1, IL-6, or TNF-α levels in the two groups before the treatment. After the treatment, the inflammatory factor levels were decreased in both groups, and the levels in the CTG were remarkably lower than they were in the MG (P<0.001), as shown in **Figure 2**.

A comparison of the renal function indexes between the two groups

There were no significant differences in the SCr, BUN, and 24 h urine protein levels between the two groups before the treatment (P>0.05). After the treatment, the three levels (SCr, BUN, and 24 h urine protein) were reduced notably in both groups (P<0.001), and the three levels in the CTG were remarkably lower than they were in the MG (P<0.001), as shown in **Table 3**.

Table 2. Comparison of the general patient data

Group	Combination therapy group (n=48)	Monotherapy group (n=48)	X^2/t	P
Gender				
Male	27 (56.25)	22 (45.83)	1.042	0.307
Female	21 (43.75)	26 (54.17)		
Age (years)	49.6±9.4	51.2±8.6	0.870	0.387
BMI (kg/m^2)	21.52±2.25	22.04±2.11	1.168	0.246
Course of the disease	4.72±1.86	4.83±1.91	0.286	0.776
Pathological type				
Capillary hyperplastic glomerulonephritis	17 (35.42)	19 (39.58)	1.095	0.578
Membranous glomerulonephritis	11 (22.92)	7 (14.58)		
Mesangial proliferative glomerulonephritis	20 (41.66)	22 (45.84)		
Education level				
< junior high school	28 (72.22)	21 (0.00)	2.043	0.153
≥ junior high school	20 (27.78)	27 (0.00)		
Residence				
City	28 (58.33)	25 (52.08)	0.379	0.616
Countryside	20 (41.67)	23 (47.92)		
Smoking history				
With	23 (47.92)	27 (35.00)	0.668	0.414
Without	25 (58.18)	21 (65.00)		
Drinking history				
With	19 (39.58)	22 (45.83)	0.383	0.536
Without	29 (60.42)	26 (54.17)		

A comparison of the clinical efficacy in the two groups

The clinical efficacy of the two groups of patients after three months of treatment was evaluated using the clinical efficacy evaluation criteria, and the results showed that total effective rate of the CTG was considerably higher than it was in the MG ($P<0.05$), as shown in **Table 4**.

The correlation of the IL-1, IL-6 and TNF-α levels with the clinical efficacy

A Spearman's test was used to analyze the correlations of the IL-1, IL-6, and TNF-α levels with the clinical efficacy. It was found that the expression levels of IL-1, IL-6, and TNF-α were all positively related to clinical efficacy. By plotting a scatter plot, it was found that the clinical efficacy was gradually improved with a decrease in the IL-1, IL-6, TNF-α levels **Figure 3**.

Discussion

CGN is a complex immune renal disease with inflammatory properties. It can lead to structural damage of glomerulus and other renal tissues, and it is the most common cause of chronic renal failure [14]. CGN becomes refractory nephropathy due to different pathological changes, the long course of the disease, easy recurrence, great harm and different prognosis [15]. A common clinical symptom of CGN, hypertension can lead to progressive renal damage [16]. Hypertension in CGN patients is related to urinary sodium excretion, glomerular tumefaction, and renal fibrosis [17]. CGN patients should receive treatment as soon as possible, including blood pressure control, especially renin-angiotensin-aldosterone system inhibitor drugs, diuretics and a low sodium diet to prevent the progression to more serious chronic kidney disease [18]. In order to find a more effective drug therapy, benazepril and losartan potassium were applied to treat CGN patients to study the effects of the combined therapy on patients' immune function, inflammatory response, and renal function.

The immune response and the inflammatory response are common pathogeneses of CGN, and they can be treated using anti-inflammato-

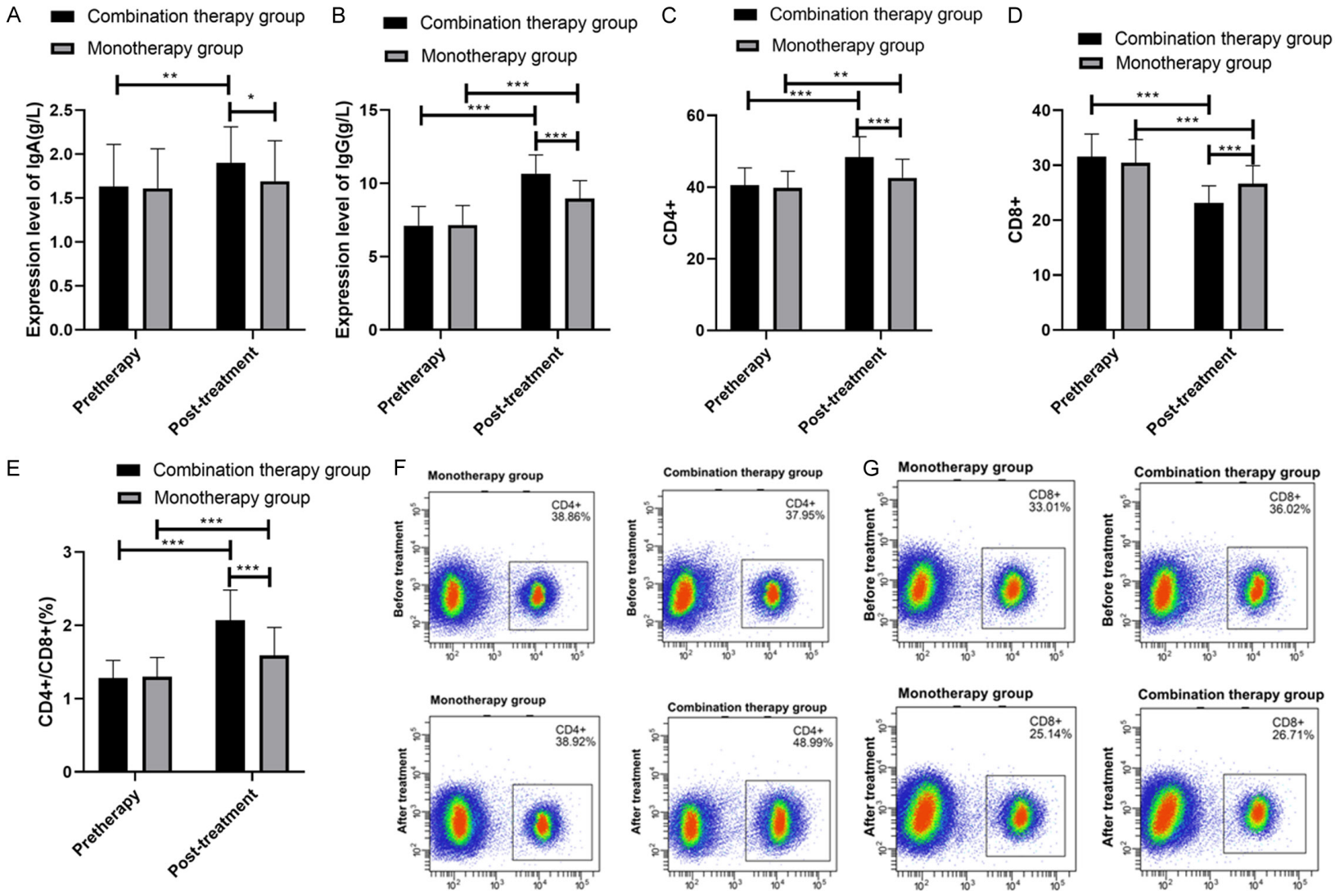

Figure 1. Comparison of the immune function indexes in the two groups before and after the treatment. A. There was no significant differences in the IgA levels between the two groups before the treatment. The IgA level in the combination therapy group was notably higher than it was in the monotherapy group after the treatment, and in the combination therapy group it was notably higher than it was in the monotherapy group. B. There was no significant difference in the IgG levels between the two groups before the treatment. The IgG levels increased notably in both groups, and in the combination therapy group the level was notably higher than that it was in the monotherapy group. C. There was no significant difference in the CD4+ levels between the two groups before the treatment. The CD4+ levels increased notably in both groups, and the level in the combination therapy group was notably higher than it was in the monotherapy group. D. There was no signifi-

cant difference in the CD8+ levels between the two groups before the treatment. The CD8+ levels decreased notably in both groups, and the level in the combination therapy group was notably lower than it was in the monotherapy group. E. There were no significant differences in CD4+/CD8+ levels between the two groups before the treatment. The CD4+/CD8+ levels increased notably in both groups, and the levels in the combination therapy group were notably higher than they were in the monotherapy group. F. Two sets of CD4+ flow cytometry. G. Two sets of CD8+ flow cytometry. * denotes P<0.05, ** denotes P<0.01, *** denotes P<0.001.

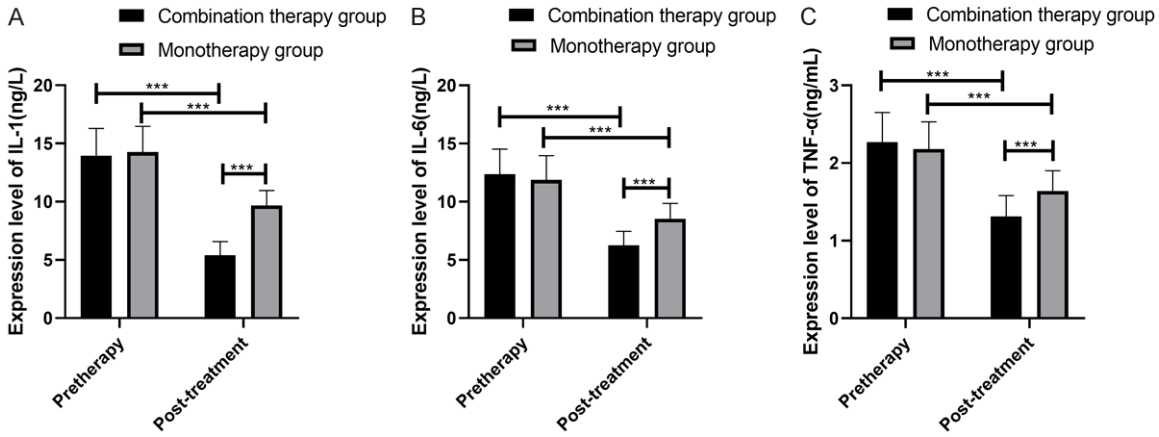

Figure 2. A comparison of the inflammatory factor levels between the two groups before and after the treatment. A. There was no significant difference in the IL-1 level between the two groups before the treatment. The IL-1 level decreased notably in both groups, and the level in the combination therapy group was notably lower than it was in the monotherapy group. B. There was no significant difference in the IL-6 level in the two groups before the treatment. The IL-6 level decreased notably in both groups, and the level in the combination therapy group was notably lower than it was in the monotherapy group. C. There was no significant difference in the TNF-α level between the two groups before the treatment. The TNF-α level decreased notably in both groups, and the level in the combination therapy group was notably lower than it was in the monotherapy group. *** denotes P<0.001.

Table 3. A comparison of the renal function indexes between the two groups

Group	SCr (μmol/L)		BUN (mmol/L)		24 h urine protein	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combination therapy group (n=48)	153.78±11.56	68.24±5.93*	8.82±1.26	3.15±0.81*	1.78±0.41	0.52±0.21*
Monotherapy group (n=48)	151.44±10.83	93.72±8.05*	8.75±1.17	5.08±0.92*	1.71±0.24	0.78±0.24*
t	1.023	17.66	0.121	10.91	1.021	5.649
P	0.309	<0.001	0.904	<0.001	0.310	<0.001

Note: * means P<0.05.

Table 4. A comparison of the clinical efficacy between the two groups

Group	Recovered	Markedly effective	Effective	Ineffective	Total effective rate
Combination therapy group	21 (43.75)	15 (31.25)	8 (16.67)	4 (8.33)	44 (91.67)
Monotherapy group	12 (25.00)	14 (29.17)	10 (20.83)	12 (25.00)	36 (75.00)
χ^2					4.800
P					0.029

ry and immunosuppressive agents [19]. CGN can lead to a disorder of T lymphocyte subgroup regulation [20]. In this research, the patients in the MG received benazepril, and the patients in the CTG received benazepril combined with losartan potassium. The quantification of the immunoglobulin levels in the two groups showed that the IgA, IgG, CD4+, and CD4+/CD8+ levels in the CTG were notably higher than they were in the MG, and the CD8+

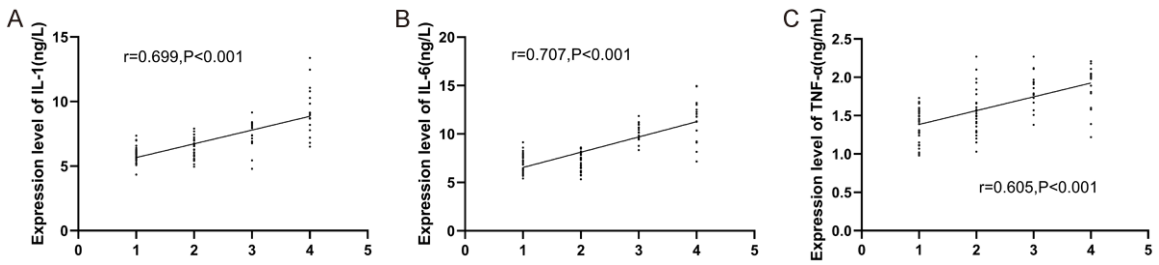

Figure 3. The correlation of the IL-1, IL-6, and TNF-α levels with the clinical efficacy. A. The expression level of IL-1 was positively correlated with the clinical efficacy (r=0.699, P<0.001). B. The expression level of IL-6 was positively correlated with the clinical efficacy (r=0.707, P<0.001). C. The expression level of TNF-α was positively correlated with the clinical efficacy (r=0.605, P<0.001).

level was considerably lower than it was in the MG. The results indicated that the CTG had a better effect on improving the immune functions of the CGN patients than the MG. Immune dysfunction is an important factor that causes CGN. Immune-mediated injury usually causes an inflammatory reaction, and immune-mediated inflammation is the main cause of CGN. Immune complexes deposit in the glomerulus or activate some immune pathways to trigger tissue injuries [21, 22]. In this study, the immunoglobulin levels of the patients in the CTG were improved, and their T lymphocyte subsets tended to be stable. A possible reason is that benazepril and losartan potassium cooperated to expand the capillary vessels in the glomerulus and to stabilize the glomerular filtration function. The two drugs also regulated the RAS system and reduced further renal fibrosis, thus protecting the kidneys and improving the immune function. Then we measured the levels of the inflammatory factors in both groups and found that the IL-1, IL-6, and TNF-α levels were notably reduced in both groups after the treatment, and the three levels in the CTG were considerably lower than they were in the MG, suggesting that the CTG could effectively reduce the inflammatory response of CGN. The renal extracellular matrix function of CGN patients is abnormal, accompanied by severe renal fibrosis, and the body is at a high level of inflammation [23]. The results of this study show that the combined use of the two drugs can improve the patients' immune functions more significantly, thus reducing the immune-mediated inflammatory response.

CGN patients are mainly young and middle-aged. CGN's clinical symptoms include edema, urinary protein, hypertension, hematuria, etc. [24]. After this treatment, the SCr, BUN and 24 hour urine protein levels in the two groups were notably lower than they were before the treatment, and the levels of the three in the CTG were significantly lower than they were in the MG, suggesting that CTG had a better effect on renal function improvement. ACEI and ARB are two major classes of RAS inhibitors, and they are believed to provide better renal protection than other types of antihypertensive drugs [25-28]. Studies have found that patients receiving ACEI have a lower risk of proteinuria than patients receiving ARB [29]. In this study, the combined treatment of the two drugs has effectively reduced patients' glomerular vascular pressure and regulated the permeability of the glomerular filtration membrane, thus reducing proteinuria and improving renal function. Finally, we found that the CTG's total effective rate was notably higher than the MG's total effective rate by evaluating the clinical efficacy of the two groups after three months of treatment, which further demonstrates that the combined use of the two drugs has a high clinical efficacy and is worthy of clinical promotion. A Spearman's test analysis showed that the clinical efficacy gradually changed with a decrease in the IL-1, IL-6 and TNF-α levels, indicating that the inflammatory factors levels were bound up with the pathological changes of CGN and might have a certain curative effect prediction value. The increased expression of the inflammatory factors in CGN patients is probably caused by oxidative stress, inflammatory reactions, and excessive body fluids. At the same time, a reduction in the clearance rate of the inflammatory factors and an accumulation of the inflammatory factors may also be caused by renal function damage. As treatment progresses, renal function is also improved, the inflammatory reaction is reduced, and the inflammatory factor level is reduced.

The findings of this study provide a certain reference value for the treatment of CGN. However, the molecular mechanism of the combination therapy of benazepril and losartan potassium remains unclear, so it needs further exploration in future studies.

Conclusion

To sum up, benazepril combined with losartan potassium treatment can effectively improve the immune function of CGN patients, reduce the inflammatory response, improve renal function, and increase the treatment effectiveness rate.

Disclosure of conflict of interest

None.

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