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Original Article

Effects of standard treatment combined with leflunomide and glucocorticoids on urinary protein, serum creatinine and urea nitrogen levels in patients with chronic nephritis: a comparison study

Xiuqin Yang[1], Qingning Bai[1], Haiying Guo[1], Yanguo Li[1], Haijun Liu[2]

[1]*Department of Nephrology, Linyi People's Hospital, Linyi, Shandong Province, China;* [2]*Shandong Medical College, Linyi, Shandong Province, China*

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Abstract: Objective: To investigate the effects of additional leflunomide and glucocorticoids on urinary protein, serum creatinine and urea nitrogen levels in patients with chronic nephritis. Methods: Eighty patients with chronic nephritis who were treated in our hospital from May 2004 to May 2006 were randomly divided into standard treatment (ST) group and ST combined with leflunomide and glucocorticoids treatment (LG) group (n=40 for each group) for four months. Inter-group differences in clinical efficacy and the incidences of adverse events were compared. Results: Compared with ST, patients receiving LG treatment showed lower urinary protein, serum creatinine and urea nitrogen levels (P=0.016, 0.021 and 0.014 respectively). Total remission rate (97.5%) in the LG group was significantly higher than that in the RT group (77.5%, P=0.023). The incidence of adverse reactions (7.5%) in LG group was lower than that in the RT group (22.5%, P=0.036) and five-year and ten-year survival rates in the LG group were significantly higher than those in the LG group (P=0.041 and 0.026 respectively). Conclusion: Leflunomide, glucocorticoids combined with ST was more effective and safer for patients with chronic nephritis compared with ST.

Keywords: Leflunomide, glucocorticoids combined with standard treatment, chronic nephritis, urinary protein, serum creatinine, urea nitrogen

Introduction

The course of chronic nephritis is markedly affected by the pathological nature of lesions with years or even decades from the first appearance of urine abnormality to chronic renal failure. Hypertension, improper diet, persistent proteinuria derived from nephritis can further fasten the natural course. Therefore, once diagnosed, nephritis should be treated timely and effectively [1]. Traditional drugs including platelet aggregation inhibitors, angiotensin converting enzyme inhibitors *etc.* can improve renal functions of patients with chronic nephritis, but the effects were far from satisfactory and some patients discontinued treatment due to adverse reactions [2].

Leflunomide is an immune-modulator which could hinder the progress of nephritis and inhibit proliferation of mesangial cells. Meanwhile, it could stimulate immunocompetent cells to produce cytokines and antibodies through regulating DNA replication and RNA synthesis. That is, leflunomide could simultaneously increase the number of immunocompetent cells and preserve the normal renal cells. Leflunomide has been found to be able to restore serum creatinine and urinary protein levels in patients with chronic nephritis [3].

The pharmacological effects of glucocorticoids vary with the dosage and routes of administration. When used at high dosage, glucocorticoids can bind to both high-affinity and low-affinity membrane receptors to exert rapid biochemical effects and non-genomic effects. Glucocorticoids at low dosage mainly acts through classic genomic effects with low onset of actions [4]. When glucocorticoids are used for treating chronic nephritis, it can alleviate the injuries of renal cells by immune complex deposition through inhibition of communications among immune cells and following immune

responses. Moreover, steroids can inhibit the degradation of polysaccharides to protect the intercellular matrix, inhibit the production of prostaglandin to suppress the activity of platelet factors, inhibit the release of nephrotoxic factors and exert anti-inflammation [5].

In this study recruiting 80 patients from our hospital between May 2004 and May 2006, we tested the effects of standard care plus combined leflunomide and glucocorticoids treatment on chronic nephritis and found that the additional use of leflunomide and glucocorticoids could more effectively treat nephritis and reduce the occurrence of adverse events.

Materials and methods

Patients

This study was approved by the ethics committee of our hospital. Eighty patients with chronic nephritis treated in our hospital from May 2004 to May 2006 were selected. All the patients met the following criteria: 1) Chronic nephritis diagnosed with clear criteria; 2) Consciousness and normal expressive capacity; 3) Informed consent signed [6]. Patients with one of the following conditions were excluded: 1) Secondary glomerular disease; 2) Tumor; 3) A history of immunosuppressors use; 4) Women in pregnancy or breast-feeding.

These patients were divided into standard treatment (ST) group and ST combined with leflunomide and glucocorticoids treatment (LG) group (n=40 for each group) using a random number table.

Intervention

Standard treatment: Patients in the ST group received ST alone. Briefly, blood pressure was maintained at normal and disturbances of water and electrolyte were cured. If acute renal failure existed, the patients switched to low-protein diet. The drugs included 10 mg of benazepril hydrochloride (Beijing Novartis Pharmaceutical Co., Ltd.) and 75 mg of dipyridamole (Suzhou Changzheng-Xinkai Pharmaceutical Co., Ltd.) daily for 4 months.

ST combined with leflunomide and glucocorticoids treatment: Besides the above-mentioned ST, patients in the LG group further received prednisone (Anyang Huaan Pharmaceutical Co., Ltd.) and leflunomide (Suzhou Changzheng-Xinkai Pharmaceutical Co., Ltd.). Prednisone was taken orally by the patients once a day at an initial dose of 0.5 mg/kg for the first month and 0.25 mg/kg for the following three months. Leflunomide was taken at a dose of 30 mg for the first 3 days and 20 mg during the rest treatment course. The urinary protein levels were strictly monitored during treatment.

Outcome measures: The levels of urinary protein, serum creatinine and urea nitrogen in patients in two groups were measured one day before and one day after treatment and compared. Adverse reactions included gastrointestinal discomfort, edema, impaired glucose tolerance, leukopenia etc. during treatment were recorded. At the end of treatment, the therapeutic efficacy was evaluated according to the criteria by the Guideline of Clinical Research of New Chinese Medicine in the Treatment of Chronic Nephritis. Briefly, if the symptoms completely disappeared, 24-hour urinary protein remained below 200 mg, red blood cells did not exist in urine under high power microscopy examination and renal function returned to normal, the therapeutic efficacy was determined as complete remission (CR). If the symptoms largely disappeared, 24-hour urinary protein reduced by more than 50% compared to before, red blood cell count did not exceed three in urine under high power microscopy examination and renal function was normal, the therapeutic efficacy was determined as general remission (GR). If t24-hour urinary protein reduced by 25% to 50% compared to before, red blood cell count ranged between 3 and 5 in urine under high power microscopy examination and renal function showed improvement, the therapeutic efficacy was determined as partial remission (PR). Otherwise, the therapeutic efficacy was determined as no remission (NR) [7]. The total remission rate was a sum of CR, GR and PR. The patients were followed-up for up to 10 years after treatment. The survival rates at 1, 5 and 10 years after treatment were compared.

Statistical analysis: SPSS20.0 Software package was used to analyze data. Urinary protein, serum creatinine, urea nitrogen level and other measurement data in the two groups were expressed as mean ± standard deviation (mean ± sd). Two-way ANOVA with repeated measures analysis accompanied with post hoc Bonfer-

Table 1. Patient demographics in two groups

Group	Cases	Gender		Age (years old)	Course of disease (years)	Disease type		
		Male	Female			MTMMPN	FSG	MN
ST group	40	21	19	37.3±14.4	3.4±1.4	18	13	9
LG group	40	20	20	38.1±14.0	3.9±1.3	19	11	10
χ^2	-	2.71		1.886	1.638	4.61	-	-
P	-	0.156		0.238	0.241	0.325	-	-

Note: MTMMPN: Mild-to-moderate mesangial proliferative nephritis; FSG: Focal segmental glomerulosclerosis; MN: Membranous nephropathy.

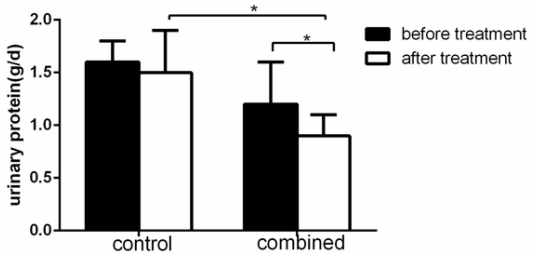

Figure 1. Comparison of the changes of urine protein level before and after treatment in two groups. Control: ST group; combined: LG group; *P<0.05.

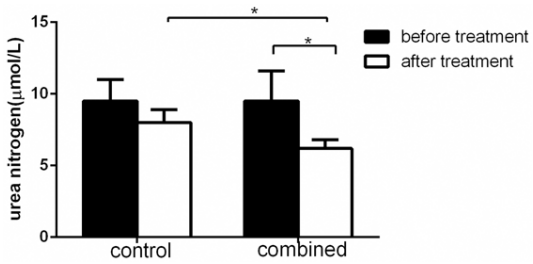

Figure 2. Comparison of the changes of urea nitrogen level before and after treatment in two groups. Control: ST group; combined: LG group; *P<0.05.

roni's test were performed to detect the effects of treatment and time on urinary protein, serum creatinine and urea nitrogen levels. The clinical efficacy, survival rate and incidences of adverse reactions were expressed as rate (%) and compared by χ^2 test. A *P* value less than 0.05 was considered statistically significant.

Results

Patient characteristics

The demographics of patients in two groups were similar. No difference was found for age, sex, nephritis duration and the pathological type (**Table 1**).

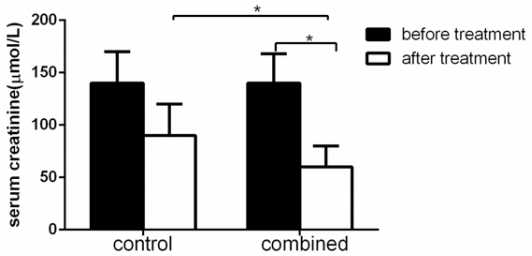

Figure 3. Comparison of the changes of serum creatinine level before and after treatment in two groups. Control: ST group; combined: LG group; *P<0.05.

Urinary protein, serum creatinine and urea nitrogen levels

After treatment, both groups showed decreased urinary protein, serum creatinine and urea nitrogen levels compared to baseline (**Figures 1-3**). Urinary protein, serum creatinine and urea nitrogen levels in LG group after treatment were significantly lower than those in RT group (P=0.016, 0.021 and 0.014 respectively).

Clinical efficacy

The total remission rate in the LG group was 97.5%, which was higher than that of the ST group (77.5%, P=0.023, **Table 2**).

Incidences of adverse events

The incidence of adverse reaction was 7.5% in the LG group, which was lower than that in the ST group (**Table 3**).

One-year, five-year and ten-year survival

The five-year and ten-year survival rate of the patients in ST group were significantly higher than those of the patients in RT group (P=0.041, 0.026 respectively). There was no significant difference in the one-year survival rate between groups (P=0.534, **Table 4**).

Table 2. Clinical efficacy between the patients of two groups (case/%)

Group	Cases	Complete remission	Initial remission	Partial remission	Non-remission	Total remission
LG group	40	15 (37.5)	14 (35.0)	10 (25.0)	1 (2.5)	39 (97.5)
ST group	40	12 (30.0)	11 (27.5)	8 (20.0)	9 (22.5)	31 (77.5)
χ^2	-	-	-	-	-	13.96
P	-	-	-	-	-	0.023

Table 3. Comparison of the occurrence of adverse reactions between the two groups of patients (case/%)

Group	Cases	Gastrointestinal discomfort	Edema	Abnormal urine sugar amount	Decreased white blood cell count	Total occurrence
LG group	40	2 (5.0)	0 (0)	0 (0)	1 (2.5)	3 (7.5)
ST group	40	3 (7.5)	2 (5.0)	3 (7.5)	1 (2.5)	9 (22.5)
χ^2	-	-	-	-	-	11.14
P	-	-	-	-	-	0.036

Table 4. Comparison of one-year, five-year and ten-year survival condition of two groups of patients (case/%)

Group	The number of cases	One year	Five years	Ten years
LG group	40	39 (97.5)	35 (87.5)	30 (75.0)
ST group	40	37 (92.5)	29 (72.5)	24 (60.0)
χ^2	-	1.32	9.35	12.83
P	-	0.534	0.041	0.026

Discussion

Chronic nephritis is not an independent disease. Most of the nephritis was caused by immunocomplex which could be soluble immune complex deposited in the glomeruli, or glomerular immune complex composed by in situ antigen and antibody [8]. Some cases of nephritis were caused by complement system activation and following inflammation by local metabolites and bacterial toxins [9, 10]. Due to that the main pathogenesis is immune inflammation, further use of leflunomide combined with glucocorticoid besides routine treatment may be more effective [11]. To confirm this, this study explored the effects of leflunomide combined with glucocorticoid on urinary protein, serum creatinine and urea nitrogen levels, clinical efficacy, the occurrence of adverse reactions and the survival of one year, five years and ten years in patients with chronic nephritis.

Studies have shown that during the treatment of chronic nephritis, leflunomide combined with glucocorticoids could enhance the overall efficacy and effectively reduce levels of 24-hour urinary protein, urea nitrogen, serum creatinine, *etc.* and reduce the incidence of adverse reactions [12]. In the acute stage of chronic nephritis, short-term treatment of leflunomide combined with glucocorticoids could effectively control the disease progression [13-15]. The results of this study showed that the levels of urinary protein, serum creatinine and urea nitrogen of patients in the ST group were significantly lower than those of before treatment. Furthermore, the post-treatment levels of urinary protein, serum creatinine and urea nitrogen of patients in the ST group were remarkably lower than those in the LG group, which was consistent with the above results and indicated that leflunomide combined with glucocorticoid could effectively improve the patient's renal function. We also found that the total remission rate and the five-year and ten-year survival rate of the LG group were significantly higher than those of the ST group and the incidence of adverse reaction was lower than that of the ST group. These results suggested that leflunomide combined with glucocorticoid could increase the total remission rate and the five-year and ten-year survival rate of patients with chronic nephritis with increased safety. According to the earlier reports, in the treatment of chronic nephritis, leflunomide combined with glucocorticoids might lead to constitutional abscess, angina, tachycardia, gall-stone, gingivitis, central obesity, edema and other drug-related side effects [16]. Therefore, if severe combined immunodeficiency or infection, peptic ulcer or lack of good bone marrow development existed in patients with chronic nephritis, leflunomide combined with glucocorticoids should be avoided [17]. These serious adverse drug reactions were not found in this study.

Leflunomide, a new immunosuppressor, has been widely used in the treatment of anaphylactic purpura nephritis and lupus nephritis. It mainly acts through inhibiting tyrosine kinase and dihydrogen lactate dehydrogenase activity, restraining the activation of T and B lymphocytes and lymphocyte proliferation, thereby inhibiting the production of antibodies and cytokines which play an essential role in immune responses [18]. Although glucocorticoids alone can promote the reduction of proteinuria levels, when used at high-dose, steroids are related with serious adverse reactions, which hinder the wide clinical use [19]. Leflunomide combined with glucocorticoids could reduce both the dosage of the steroids used and the incidences of adverse reactions, thereby significantly increasing patients' tolerance [20].

In conclusion, leflunomide combined with glucocorticoid can effectively reduce the levels of urinary protein, serum creatinine and urea nitrogen in patients with chronic nephritis. However, this study had a small sample size and the results might not be very representative, which required further large-sized studies to verify these results.

Disclosure of conflict of interest

None.

Address correspondence to: Haiying Guo, Department of Nephrology, Linyi People's Hospital, No. 48 Jiefang Road, Lanshan District, Linyi 276000, Shandong Province, China. Tel: +86-0539-8216-273; E-mail: guohaiyingkaa@126.com

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