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The Effect of Rituximab assisted Prednisone and Cyclophosphamide on the Treatment of Idiopathic Membranous Nephropathy and Its Influence on Serum Nephrin and BAFF Levels

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YJ and XT collected the samples. YJ and HC analysed the data. XT and HC conducted the experiments and analysed the results. All authors discussed the results and wrote the manuscript.

Key words
Rituximab, Prednisone, Cyclophosphamide, Idiopathic membranous nephropathy, Nephrin, BAFF00

ABSTRACT

The aim of this study was to explore the effect of rituximab-assisted prednisone and cyclophosphamide on the treatment of idiopathic membranous nephropathy (IMN) and its influence on serum levels of nephrin and B-cell activation factor belonging to the TNF family (BAFF). For this purpose, a prospective randomized controlled study method was designed for this study. 92 patients with IMN in our hospital from December 2015 to December 2017 were divided into study group (n=46) and control group (n=46) based on a computer-generated random number table. On the basis of conventional treatment, the control group was given prednisone and cyclophosphamide treatment, and the study group was given rituximab-assisted prednisone and cyclophosphamide treatment, both of which were treated for 6 months. The efficacy, adverse reactions, and recurrence rates of 1 and 2 years after treatment, clinical symptom scores and renal function indices such as urine protein quantification (Upro), blood creatinine (Scr), urea nitrogen (BUN)), serum albumin (ALB), nephrin, and BAFF levels before treatment, 3 months after treatment, and 6 months after treatment were compared between the 2 groups. Results showed that after treatment, the total effective rate of the study group was 93.48% higher than that of the control group 76.09% (P<0.05). The clinical symptom scores of the two groups were lower than those before treatment, and the score of study group was lower than that of the control group after 3 and 6 months of treatment (P<0.05). The 24h levels of Upro, serum Scr, BUN, and BAFF after 3 months and 6 months of treatment in the two groups were lower than those before treatment. The levels of the study group were lower than those of the control group. The serum ALB and nephrin levels were higher than those before treatment. The levels of the study group were higher than those of the control group (P<0.05). The two-year recurrence rate of the study group was 9.09% lower than that of the control group 25.00% (P<0.05). There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). To conclude, the application of rituximab-assisted prednisone and cyclophosphamide in the treatment of IMN can improve serum nephrin and BAFF levels, reduce clinical symptoms, improve renal function and curative effect, and reduce recurrence rate, and is safe.

INTRODUCTION

Idiopathic membranous nephropathy (IMN) is a common nephrological. Its clinical symptoms include edema, albuminuria, hypoproteinemia and high blood pressure. It is difficult to treat, and may deteriorate to the end stage of kidney disease with the progress of the disease, thus endangering the life of patients (Huang *et al*., 2018; Zou *et al*., 2018; Kim *et al*., 2019). Prednisone and cyclophosphamide are common drugs for the treatment of IMN. They can alleviate clinical symptoms and reduce proteinuria, but they have many adverse reactions and low remission rate (Guo *et al*., 2019; Zhang *et al*., 2017). Recent studies have shown that B cells can participate

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in the production of glomerular subepithelial immune complexes, which damage the glomerular filtration barrier and lead to proteinuria. Selective inhibition of B cells to form pathogenic antibodies may be an important way to treat IMN (Wang *et al*., 2018). Rituximab is a CD20 monoclonal antibody on the surface of B cells, which can eliminate B cells and inhibit antibody production (Rojas *et al*., 2019). Therefore, it is speculated that the application of rituximab-assisted prednisone and cyclophosphamide in the treatment of IMN may further improve the curative effect. However, there is no such research report in clinic at present, and its exact curative effect still requires extensive research and demonstration. In this study, a prospective randomized controlled trial was conducted to analyze the effect of low-dose rituximab-assisted prednisone and cyclophosphamide in the treatment of IMN, and its influence on serum nephrin and B-cell activation factor belonging to the TNF family (BAFF).

MATERIALS AND METHODS

General data

A prospective randomized controlled study method was adopted. 92 patients with IMN in our hospital from December 2015 to December 2017 were selected. The patients were divided into study group (n=46) and control group (n=46) based on a computer-generated random number table. The general data (gender, body mass index (BMI), age, course of disease, family history, complications) of the two groups were balanced and comparable, with no significant difference ($P > 0.05$), as shown in (Table I). This study has been approved by the Ethics Committee of our hospital.

Selection criteria

Inclusion criteria

IMN confirmed by renal biopsy; age > 18 years old; typical manifestations of nephrotic syndrome, serum albumin (ALB) < 30 g/l, 24h urine protein quantification (24h Upro) > 3.5 g; aware of this research and signing the informed consent.

Exclusion criteria

Secondary membranous nephropathy caused by diabetic nephropathy, drugs, infection and other reasons; B-ultrasound examination shows that the volume of both kidneys decreases significantly; complicated with severe abnormal functions of liver, heart, lung and other organs; complicated with diseases of nervous system, blood system and immune system; complicated with malignant tumor and acute and chronic infection; recent treatment with immunosuppressor, hormones and non-steroidal anti-inflammatory drugs; allergic to the drugs used in this study.

Table I. Comparison of general data between the two groups.

Data	Control group(n=46)	Research group(n=46)	t/χ^2	P
Gender (%)				
Female	17(36.96)	19(41.30)	0.183	0.669
Male	29(63.04)	27(58.70)		
BMI(kg/m^2)	16~26 (21.53±1.96)	17~26 (21.80±2.04)	0.647	0.519
Age (years)	22~75 (50.91±9.03)	24~76 (51.42±8.26)	0.283	0.778
Course of disease (years)	1~5 (3.64±0.97)	1~5 (3.76±1.04)	0.572	0.569
Family history (%)	3(6.52)	4(8.70)	0.000	1.000
Complications (%)				
High blood pressure	17(36.96)	19(41.30)	0.183	0.669
Hyperlipidemia	9(19.57)	10(21.74)	0.066	0.797
Diabetes	9(19.57)	11(23.91)	0.256	0.613

Treatment method

Both groups were given routine treatment such as low-salt and low-fat diet, maintaining water and electrolyte balance, correcting acidosis, controlling blood pressure and infection. On this basis, the control group was given prednisone (Shanghai Sine Pharmaceutical Laboratories Co., Ltd., SFDA Approval No. H31020675) and cyclophosphamide (Jiangsu Sheng Di Pharmaceutical Co., Ltd., SFDA Approval No. H32020857): (1) Prednisone: the initial dose was 0.6 ~ 1.0 mg/(kg d), and the maximum dose was ≤60 mg/d, which was divided into (2) Cyclophosphamide: 0.5g to 1.0 g of cyclophosphamide was dissolved in 250ml to 500 ml of normal saline for intravenous drip once a month. The study group was given rituximab (Shanghai Henlius Biological Pharmaceutical Co., Ltd., SFDA Approval No. S20190021) in combination with prednisone and cyclophosphamide: (1) The treatment method and doses of prednisone and cyclophosphamide are the same as those of the control group; (2) Rituximab: 375 mg/m^2, intravenous drip, once a week, 4 times. Both groups received treatment for 6 months.

Detection method

Fasting venous blood sample (6 ml) was taken from patients in the morning. After standing for 25 min at room temperature, the sample was centrifuged for 5 min with a centrifuge at a speed of 3500 r/min and a centrifugal radius of 10 cm to extract serum. The extracted serum was

frozen in a refrigerator at-80 °C for detection. The levels of serum creatinine (Scr), urea nitrogen (BUN) and albumin (ALB) were measured by an automatic biochemical analyzer (ADVIA1800 produced by Siemens, Germany). Enzyme-linked immunosorbent assay (ELISA) was used to measure serum nephrin and BAFF levels. The kits were all purchased from Shanghai cell research Biotechnology Co., Ltd. (2) Urine samples (24 h) were taken from patients, and Upro was measured by the full-automatic biochemical analyzer (ADVIA1800 produced by Siemens, Germany). The related operations were all strictly carried out according to the instrument and kit instructions.

Observation targets

Curative effect, according to the severity (none, slight, moderate, server) of clinical symptoms (edema, back pain, foam like stool, fatigue, etc.), and the severity of clinical symptoms before treatment, 3 months and 6 months after treatment were scored 0, 2, 4 and 6 points respectively. The higher the score was the more serious the clinical symptoms are. Levels of renal function indices (24h Upro, Scr, BUN), serum nephrin and BAFF levels before treatment, adverse reactions during treatment and after treatment. the patients were followed up for 2 years by telephone and outpatient re-examination. The 1 and 2-year recurrence rates after treatment were also counted.

Evaluation criteria of curative effect

For invalid treatment, the clinical symptoms of patients are not alleviated after treatment. The 24h Upro decreases by < 50%, or the renal function deteriorates. And serum ALB level < 30 g/l; for partial remission, the clinical symptoms are obviously relieved. The 24h Upro decreases by ≥50% or is within 0.5 g to 3.5 g. The renal function tends to be stable, and the serum ALB level is within 30g/L to 34 g/L; for complete remission, the clinical symptoms disappear basically. 24h Upro is < 0.5g, and the renal function is stable. The serum ALB level is ≥35 g/L. The total effective rate is (partial remission+complete remission) /46×100% (Xue *et al*., 2019).

Statistical analysis

The research data was entered into SPSS 21.0 software for processing, and the measurement data was expressed in ($\bar{x} \pm s$). Independent sample t test was used for comparison between groups, and paired t test was used for comparison before and after treatment in this group; the counting data was expressed by n (%), and the comparison between groups was tested by χ^2 test; $P < 0.05$ indicates statistically significant.

RESULTS

Curative effect

After treatment, the total curative effect of the study group was higher than that of the control group ($P < 0.05$) (Table II).

Table II. Comparison of curative effect between 2 groups n (%).

	Control (n=46)	Expermintal (n=46)	χ^2	P
Invalid	36.52	11 (23.91)		
Partial relief	18 (39.13)	17 (36.96)		
Complete relief	25 (54.35)	18 (39.13)		
Total effective rate	35 (76.09)	43 (93.48)	5.392	0.020

Clinical symptom scores

There was no significant difference between the two groups before treatment ($P > 0.05$). After treatment for 3 months and 6 months, the clinical symptom scores of the two groups were lower than those before treatment, and the score of the study group was lower than that of the control group ($P < 0.05$), (Table III).

Renal function indices, serum ALB, serum nephrin, and BAFF levels

Before treatment, there was no significant difference between the two groups in the levels of Upro, serum Scr, BUN and ALB ($p > 0.05$). The levels of 24h Upro, serum Scr and BUN of the two groups were lower than those before treatment, and the levels of the study group were lower than those of the control group. The ALB level of the two groups was higher than that before treatment, and the ALB level of the study group was higher than that of the control group ($p < 0.05$) (Table IV).

There was no significant difference in serum nephrin and BAFF levels between the two groups before treatment ($P > 0.05$). After 3 months and 6 months of treatment, the serum nephrin levels of the two groups were higher than those before treatment, and the serum nephrin level of the research group was higher than that of the control group. The BAFF levels of the two groups were lower than those before treatment, and the BAFF level of the study group was lower than that of the control group ($P < 0.05$) (Table IV).

Adverse reactions

There was no significant difference between the two groups in the incidence of adverse reactions ($P > 0.05$) (Table V).

Table III. Comparison of clinical symptom scores between the two groups ($\bar{x} \pm s$, score).

Time	Before treatment		After 3 months of treatment		After 6 months of treatment	
Group	**Control group (n= 46)**	**Research group (n= 46)**	**Control group (n= 46)**	**Research group (n= 46)**	**Control group (n= 46)**	**Research group (n= 46)**
Edema	5.15±0.42	5.07±0.48	4.06±0.39a	3.41±0.35a	2.98±0.36a	2.54±0.29a
Back pain	3.57±0.36	3.49±0.32	2.96±0.30a	2.48±0.24a	2.59±0.23a	2.24±0.19a
Foam like stool	4.35±0.48	4.26±0.52	3.20±0.42a	2.76±0.37a	2.85±0.34a	2.38±0.30a
Fatigue	5.48±0.46	5.36±0.41	3.95±0.37a	3.14±0.34a	2.87±0.31a	2.29±0.26a

Note: compared with this group before treatment, $^aP < 0.05$

Table IV. Renal function indices and serum ALB, serum nephrin and BAFF levels between the 2 groups ($\bar{x} \pm s$).

Time	Before treatment		After 3 months of treatment		After 6 months of treatment	
Group	**Control group (n= 46)**	**Research group (n= 46)**	**Control group (n= 46)**	**Research group (n= 46)**	**Control group (n= 46)**	**Research group (n= 46)**
24 h Upro(g)	7.64±0.68	7.59±0.72	3.52±0.63a	2.45±0.59a	1.52±0.46a	0.83±0.37a
Scr(μmol/L)	78.73±8.09	78.31±7.58	68.93±6.41a	64.17±6.18a	65.62±6.15a	60.29±5.74a
BUN(mmol/L)	7.60±2.28	7.49±2.06	7.04±1.36a	6.42±1.23a	6.72±1.29a	6.18±1.14a
ALB(g/L)	26.83±2.34	26.52±2.41	31.24±3.27a	35.16±3.69a	33.06±3.58a	37.82±3.95a
Nephrin(μg/ml)	21.84±4.02a	7.48±0.95	16.97±2.85	26.48±5.63a	8.52±1.03a	11.72±1.53a
BAFF(g/L)	16.52±3.39a	7.26±0.83	17.23±2.69	21.15±5.27a	10.08±1.45a	13.58±1.71a

ALB, albumin; BAFF, beta cell activating factor; BUN, blood urea nitrogen; Scr, blood creatinine; Upro, urine protein. Compared with this group before treatment, aP<0.05

Table V. Comparison of adverse reactions between 2 groups. The values are in n (%).

	Control group (n= 46)	Research group (n= 46)	χ^2	P
Feel sick and vomit	3(6.52)	3(6.52)		
Abdominal pain and bloating	0(0.00)	1(2.17)		
Elevated blood sugar	1(2.17)	1(2.17)		
High blood pressure	1(2.17)	2(4.35)		
Leukopenia	1(2.17)	1(2.17)		
Total incidence	6(13.04)	8(17.39)	0.337	0.562

Table VI. Comparison of recurrence rates between the two groups. The values are in n (%).

	1-year after treatment (n= 44)	2-year after treatment (n= 44)	χ^2	P
Number of cases	2(4.55)	6(13.64)	1.238	0.266
Research group	4(9.09)	11(25.00)	3.938	0.047
Control group	2(4.55)	6(13.64)	1.238	0.266

Note: cases of shedding have been excluded.

Recurrence rate

After 2 years' follow-up, there were two shedding cases in the study group and the control group respectively. There was no significant difference in 1-year recurrence rates of the two groups after two years' treatment ($P > 0.05$), but the recurrence rate of the study group was lower than that of the control group ($P < 0.05$) (Table VI).

DISCUSSION

IMN is an important cause of adult nephrotic syndrome, which is prone to repeated attacks with a long course of disease and poor prognosis. Without reasonable treatment, about 40% of cases can progress to end-stage renal disease within 5 to 10 years, which increases the pain of patients and brings a heavy burden to their families and the society (Yu *et al*., 2019). Hormone drugs combined with cyclophosphamide is a common treatment for IMN, which can alleviate the clinical symptoms, reduce proteinuria and protect renal function (Wu *et al*., 2019). Yu *et al*. (2018) argued that after 12 weeks of treatment with prednisone combined with cyclophosphamide, the renal function of patients with membranous nephropathy was obviously improved, and the clinical symptoms and

signs were alleviated. In this study, prednisone combined with cyclophosphamide was used to improve the renal function to some extent after IMN treatment. The total effective rate was 76.09%, which was consistent with the above study. It is suggested that prednisone combined with cyclophosphamide is effective in the treatment. However, the curative effect of this scheme needs to be further improved, and the long-term application has great side effects.

In recent years, clinical studies have pointed out that effectively preventing B-cells from forming pathogenic antibodies may be a new way to treat IMN, and giving such drugs on the basis of routine treatment can further improve the curative effect (Van den Brand *et al*., 2017). CD20 is a specific marker on the surface of B-cells, which can regulate the differentiation and maturation of B-cells by participating in calcium channel composition. Rituximab is a monoclonal antibody against CD20 on B-cell surface. Based on the retrospective study, Liu *et al*. (2019) found that rituximab can effectively reduce proteinuria and relapse of IMN patients, and is an ideal immunosuppressant for IMN treatment. Through prospective randomized controlled study, Zhang *et al*. (2019) showed that the application of rituximab can significantly improve the renal function of patients, and the total effective rate is 94.74%. In this study, the total effective rate of rituximab-assisted prednisone and cyclophosphamide was 93.48%. There was higher clinical symptom score, and more significant decrease of 24h Upro, serum Scr and BUN levels and increase of serum ALB and lower 2-year recurrence rate after treatment. It is suggested that rituximab-assisted prednisone and cyclophosphamide can alleviate clinical symptoms, improve renal function and curative effect and reduce recurrence rate. After entering human body, rituximab can bind with CD20 on the surface of B-cells, and eliminate B cells and prevent the generation of pathogenic antibodies through complement-dependent or antibody-dependent anti-proliferation effect, apoptosis induction and cytotoxicity (Zhang *et al*., 2019). It has also been reported that rituximab can regulate the steady state and function of T-cell subsets, weaken Th17 reaction, reduce the number of CD4+T cells, restore the proportion and function of regulatory T-cells, and down-regulate the expression of serum-induced acid sphingomyelinase-like phosphodiesterase 3b, thus protecting the framework and vitality of podocyte actin, avoiding podocyte decline, and finally reducing proteinuria and improving renal function (Chen *et al*., 2018).

In addition, BAFF can participate in the growth, differentiation and antibody formation of human B-lymphocytes, and induce the immune response of T-lymphocytes, playing an important role in humoral and cellular immunity. The increase of BAFF level is related to the occurrence and progress of IMN, and it may be beneficial to improve the patient's condition and prognosis by downregulating the expression of serum BAFF. The study of Guo *et al*. (2017) shows that the serum BAFF level of patients with membranous nephropathy is on the high side, and the serum BAFF level decreases after the patients' condition is improved by systematic treatment. This can provide certain reference for the evaluation of curative effect of membranous nephropathy treatment. Nephrin is a membrane protein of glomerular podocyte hiatus which can participate in the formation of glomerular filtration barrier. The decrease of Nephrin expression can damage glomerular filtration barrier and lead to the occurrence and progress of membranous nephropathy (Guo *et al*., 2019). The research of Ji *et al*. (2016) also reports that the expression of serum Nephrin in IMN patients will significantly decrease, and the expression is related to podocyte and renal function injury. This could provide a certain basis for clinical diagnosis and treatment. In this study, it was found that the serum BAFF level decreased and the serum nephrin level increased significantly after the treatment with rituximab-assisted prednisone and cyclophosphamide. The results indicate that the application of rituximab-assisted prednisone and cyclophosphamide in the treatment of IMN can improve the serum Nephrin and BAFF levels, which is consistent with the previous research and analysis that rituximab can regulate immune function, prevent podocyte injury and improve renal function (Li, 2017). In addition, this study also showed that the application of rituximab assisted prednisone and cyclophosphamide in the treatment will not significantly increase the adverse reactions, and there is good patient tolerance and drug safety during the treatment (Brian, 2018).

CONCLUSION

To sum up, the application of rituximab-assisted prednisone and cyclophosphamide in the treatment of IMN can regulate the serum Nephrin and BAFF levels, relieve clinical symptoms, improve renal function and clinical efficacy, and reduce recurrence rate, and is safe.

Statement of conflict of interest

The authors have declared no conflict of interes.

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