26 Cases of Intractable Membranous Nephropathy Glucocorticoid Combined Gilad Amine Clinical Curative Effect Observation

Si-Qi ZHANG¹,a, Rui-Si XU²,b, Jian YIN ³,c*

Nephrology, China-Japan Union Hospital of Jilin University, 126 Xiantai Street, Changchun, Jilin Province, China.
Endoscopy Center, China-Japan Union Hospital of Jilin University, 126 Xiantai Street, Changchun, Jilin Province, China.
Vascular Surgery, China-Japan Union Hospital of Jilin University, 126 Xiantai Street, Changchun, Jilin Province, China.

¹siqi@jlu.edu.cn, ²bxrs-email@163.com, ³16407026@qq.com
*Corresponding author

Keywords: Thalidomide, Refractory nephrotic syndrome, Membranous nephropathy.

Abstract. To study the clinical effect of glucocorticoid combined with thalidomide in the treatment of refractory nephrotic syndrome with membranous nephropathy. Methods: the pathological for membranous nephropathy of 26 patients with refractory nephrotic syndrome, glucocorticoid + gilad amine 50 mg 2 times/d, to turn the urine protein application again after 12 weeks after the reduction of 50 mg, l/d, maintain half year outage. The invalid was given a maximum of 24 weeks to stop the drug. The observation time was 24 weeks. Results: 24h urine protein decreased from 9.15 ±3.23 to 1.43±1.91 (P<0.01). Plasma albumin rose from 26.02 ±6.75 to 35.57 ±4.02 (P<0.01). In most cases, the onset time was between 8 and 16 weeks, with a total relief of 30.77% in 24 weeks and 50.00% in partial relief, with a total effective rate of 80.77%. The main side effects are: rash, lethargy, fatigue, dizziness. No liver and kidney damage, bone marrow suppression. Conclusion: thalidomide combined with glucocorticoid is effective in the treatment of membranous nephropathy, with mild side effects, which provides a new way for the treatment of refractory membranous nephropathy.

Introduction

Membranous nephropathy there is no unified treatment, clinical treatment is largely hormone and immune inhibitor, has obtained the certain effect, there are still some patients even many kinds of immunosuppressant share is still less than satisfactory curative effect. The pathogenesis of membranous nephropathy is both clear, in recent years, studies have shown that the immune response is the initial factor of glomerular disease, on this basis; the inflammatory mediators involved in glomerular damage caused the disease. Thalidomide appear on the market on 1950’s as sedatives, in recent years, using its immune regulation of section, cut vascular endothelial growth factor (vascular endothelial growth factor, VEGF), inhibition of tumor necrosis factor - (TNF-α) and an action such as anti-inflammatory, has been widely used in the treatment of malignant tumors, such as rheumatic autoimmune disease, and shows good curative effect [¹,²], suggesting Sally amine treatment for nephrotic syndrome. We
tried to treat the patients with refractory nephrotic syndrome treated by thalidomide in our hospital, and achieved satisfactory results. The report is as follows.

**Objects and Methods**

**Objects**

From January 2011 to December 2014, 26 patients were diagnosed with nephrotic syndrome in our hospital, including 14 males and 12 females. Age 25 ~ 74 years old, average 43.15 years old. All of them have been married and have children, and the clinic is in line with the diagnostic criteria of nephrotic syndrome. The course of treatment is 4 months to 2 years. 26 patients have the renal biopsy data, which is not typical of membranous nephropathy (clinical) found no secondary causes of 14 cases, 12 cases primary membranous nephropathy (stage I 6 cases of membranous nephropathy, H) 6 cases of membranous nephropathy). Liver function and renal function were normal before medication.

In 26 patients, the initial treatment regimen was all sufficient hormone plus cyclophosphamide or mycophenolate or cyclosporine A, and one of the following cases was treated with thalidomide. The application of the above treatment regimens for 8 ~ 12 weeks was not alleviated, and after 3 months of discontinuation of cytotoxic drugs, thalidomide was applied to 18 patients. (2) the application of the treatment of liver damage or bone marrow inhibition effects, first stop cytotoxic drugs observed 4 weeks, the original kidney disease without relief, blood routine liver function returned to normal after the application of gilad amine, a total of 6 cases; (3) effective starting treatment, urine protein quantitative fell more than 50%, but dropped to a certain degree appeared repeatedly, except other reversible cause of relapse, such as fatigue, infection, irregular withdrawal or by drugs, for 8 weeks the urine protein without falling, a total of 2 cases.

**Treatment Methods and Observation Indexes**

This experiment is in accordance with the standard of human test ethics and is approved by the ethics committee of Jilin University. All patients have signed the informed consent. The original dosage of the hormone was unchanged, and the normal hormone reduction was still followed by other auxiliary drugs. Stop using the original immunosuppressant, oral, degree of amine 50 mg 2 times/d, sleepiness significantly to 100mg patients, 1 times a night, turn to the urine protein application again after 12 weeks after the reduction of 50 mg, (qd, maintain half year outage. The invalid was given a maximum of 24 weeks to stop the drug. All patients were treated with aspirin 75mg, once a night. Blood routine, urine routine and 24h urine protein were checked every 2 weeks during the first 3 months of the medication, and liver and kidney function, electrolyte and lipid were checked every 4 weeks. After 3 months, the above indicators were detected every 4 weeks, and the side effects of the drug were observed, and the observation time was 24 weeks.

**Criteria for Efficacy Determination**

1. **Total remission**: 24h urine protein quantitation <0.3g, normal renal function, normal blood albumin, and disappearance of clinical symptoms; 2. **Partial remission**: 24h urine protein quantification decreased >50%, albumin increased before treatment, but did not reach normal, renal function was normal, with mild edema; 3. **Disable**: the clinical symptoms of 24h urinary
protein were less than 50% or renal failure, blood albumin <30g/L, and no improvement in clinical symptoms; ④ Relapse: the treatment process has been effective for various reasons for the elevation of urinary protein.

Statistical Methods

SPSS 16.0 statistical software was used for analysis, and t-test was used in the measurement data group.

Result

Changes of Urine Protein and Plasma Albumin

Beginning for a long time, there are 3 cases of 4 weeks began to appear, all cases of observing the urine protein quantitative (9.01 ± 2.25 vs 9.15 ± 3.23, P > 0.05) and plasma albumin (26.02 ± 6.75 vs 28.02 ± 6.75, P > 0.05) was no obvious change, the three patients also appear urine protein was increased, the then alleviate disease cases gradually increased, starting to pay off time in most of the cases in 8 ~ 16 weeks, ease to 16 weeks 13 cases, and there are 6 cases achieved complete remission. At the end of 24 weeks, urinary protein quantification decreased significantly, and 24h urinary protein decreased from 9.15 ± 3.23 to 1.43 ± 1.91 (P<0.01).

Renal Function, Liver Function and Routine Blood Changes

 Serum creatinine and urea and uric acid were not significantly changed (P> 0 0.05). Liver function: aspartate aminotransferase, alanine aminotransferase showed no significant change (P > 0.05); Blood routine: erythrocyte and platelet count did not change significantly, the white blood cells began to increase gradually, and as the hormone reduction gradually returned to normal, the consideration was related to the application of hormones.

Side-effect

There were 4 cases of skin rash, mainly manifested as facial and body papules, accompanied by pruritus, which occurred at 2~4 weeks after taking oral antihistamine, and continued treatment. There were 4 cases of narcolepsy and anemic symptoms, which occurred about 1 week after taking the drug and changed to 100mg, qd, and the symptoms were significantly relieved. Dizziness 2 cases, with time extension, self - relief. Two cases showed numbness in the hands, reduced to 50mg,qd, and decreased after oral vitamin B. No liver function damage, bone marrow suppression.

Discussion

Thalidomide degrees amine is a kind of sedative analgesics, not the barbiturates for treatment of pregnancy nausea and vomiting are widely used in clinical effect is remarkable in the 50 s, but soon because of the serious birth defects and withdrawn from the market. Recent studies have found that this drug can increase tnf-α mRNA degradation and down-regulate the expression of tnf-α. Prevent important activating TNF -α factor NF - B Κ activation, thus reducing the production of TNF-α[3,4]. Studies have shown that thalidomide can reduce serum and synovial tissue VEGF and TNF-α expression in arthritis rats. A significant number of experiments showed that thalidomide significantly inhibited VEGF secretion and angiogenesis.
and increased apoptosis. It has been found that oral thalidamine can inhibit the expression of bFGF in rabbit corneal basic fibroblast growth factor, in order to reduce the formation of rabbit corneal blood vessels[5]. So at present, thalidomide has been used in the treatment of systemic lupus erythematosus and rheumatoid arthritis, which has achieved good curative effect, and it has been found to reduce the urinary protein of lupus nephritis.

Nephrotic syndrome pathogenesis is unclear, immune-mediated inflammatory response may as its key link, including cytokines, such as: TNF-α, VEGF, interleukins, play an important role in the onset of nephrotic syndrome the weight of the disease was closely related with the exception of cytokines, especially cytokines IL - 6, IL - 8 and TNF -α, them as inflammatory mediators involved in glomerular disease free of pest damage process P1.Reports VEGF can affect the glomerular filtration membrane charge barrier, with endothelial cell receptor, the endothelial cell rupture, local ACTS on glomerular mesangial area, can cause glomerular volume increase, to some cytokines. VEGF is closely related to proteinuria and urinary protein levels.

According to its pathogenesis, this study choose a variety of immunosuppressive treatment is invalid or because of all sorts of side effects cannot be applied at present commonly used immunosuppressant nephrotic syndrome patients with membranous nephropathy, Sally degrees amine treatment observation of 26 cases, obvious effect, until the end of observing 24 weeks, completely relieve 8 cases, accounted for 30.77%, partial in 13 cases, accounting for 50.00%, total effective rate was 80.77%.

But we observe observe working time is slow, part 4 weeks only three patients relieve, there are 3 patients without fatigue induced factors such as infection, the urine protein high, adhere to the medication to 12 weeks when the majority of patients to a drop in the urine protein, one is the group of patients are intractable membranous nephropathy, namely the current commonly used immunosuppressant invalid or hormone immunosuppressant therapy for memory. Second, membranous nephropathy is also slow in the application of other immunosuppressive agents, and whether the third is related to the small dose of thalidomide, and we are prepared to increase the dosage of the drug. The maximum number of tumor chemotherapy was reported to 1000mg/d.

The common adverse reaction of thalidomide is to cause fetal malformation, and the patient should avoid pregnancy during medication. Secondly there are multiple neuritis, constipation, fatigue, sleepiness, orthostatic hypotension, dizziness, skin rash, neutrophil decrease, this study found that this group of patients are the most common side effects of mild lethargy, lack of power, followed by a rash, other side effects did not appear in this group of patients. Monitoring during treatment the patient blood routine, liver function, renal function, blood sugar, found no apparent change, in addition, the application of glucocorticoid, a large amount for a long time before including refractory determine medication observation, as a result of long-term side effects, such as femoral head necrosis, adrenocortical hypofunction, etc., as the extension of treatment time will happen, remains to be further tracking.

References


