Effect of recombinant human thrombopoietin on IL-2, IL-4 and platelet parameters in thrombocytopenic purpura

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ABSTRACT

The objective of this study was to observe the effect of recombinant human thrombopoietin on IL-2, IL-4 and platelet parameters in thrombocytopenic purpura. For this purpose, a convenient sampling method was used to select 84 patients with thrombocytopenic purpura who visited the hospital from January 2018 to December 2022. The patients were divided into the norm group and rhTPO group with 42 cases each by random number table. The norm group was treated with routine treatment, while the rhTPO group was treated with recombinant thrombopoietin based on routine treatment. The changes in IL-2, IL-4, platelet parameters, immune recovery and treatment efficiency of the two groups were compared before and after treatment. Findings suggested that the levels of IL-2 and IL-4 in both groups decreased after treatment compared with those before treatment. However, the level of IL-2 in the rhTPO group after treatment was lower than that in the norm group, and the level of IL-4 in the rhTPO group after treatment was higher than that in the norm group (P<0.05). The levels of platelet parameters PLT and PCT in the two groups after treatment were higher than those before treatment, but the levels of PLT and PCT in the rhTPO group after treatment were higher than those in the norm group (P<0.05). The PLT of the rhTPO group was $(69.57\pm6.73)\times10^9$/L after 7 days of treatment, which was higher than that in the norm group $(62.05 \pm 8.52)\times10^9$/L (P<0.05). The levels of PDW and MPV in the two groups after treatment decreased compared with those before treatment, but the levels of PDW and MPV in the rhTPO group after treatment were lower than those in the norm group (P<0.05). The overall immune recovery and treatment effectiveness of the rhTPO group were significantly better than those of the norm group. In summary, recombinant human thrombopoietin used in patients with thrombocytopenic purpura can maintain the balance between T cell activation and inhibition homeostasis, and promote faster recovery of platelet parameters.

Introduction

Thrombocytopenic purpura (TP) is mainly characterized by decreased platelet count and bleeding of skin, mucosa and organs, belonging to hematological diseases. It has multiple types of idiopathic, immune and thrombotic. TP can cause the reduction of platelet production, and aggravate the abnormal blood coagulation function of the body, thus leading to serious organ bleeding, and even endangering life. At the same time, immune and thrombotic TP often occur at the same time (1). Clinically, TP is mainly treated by immunoglobulin, glucocorticoid, gamma globulin, platelet suspension infusion and plasma exchange (2). However, these treatment methods still have problems of easy recurrence and poor prognosis, and even lead to some patients evolving into refractory TP patients (3,4). In recent years, recombinant human thrombopoietin (rhTPO) has formed a clinical advantage of first-line adjuvant and second-line treatment of TP. From the perspective of the pathological mechanism of TP, the occurrence of TP is related to the imbalance of Th1/Th2 cells in patients. IL-2 and IL-4 represent Th1 cells and Th2 cells respectively (5). Its clinical changes can reflect the balance of Th1/Th2 cells. Platelet parameters can provide feedback on the body's thrombocytopenia (6,7). IL-2, IL-4 and platelet pa-

rameters can form an objective quantitative effect on the clinical efficacy of patients with TP after treatment. They are also the monitoring means of TP treatment. Research shows that rhTPO is suitable for the treatment of refractory idiopathic TP and can improve the platelet (8). However, whether rhTPO can affect the IL-2, IL-4 and platelet parameters of TP patients needs further study. The purpose of this study is to determine the effect of rhTPO on IL-2, IL-4 and platelet parameters of TP patients by means of a clinical controlled study. The results are reported as follows.

Materials and Methods

General information

A convenient sampling method was used to select 84 TP patients who visited the hospital from January 2018 to December 2022. The patients were divided into the routine group (NG) and rhTPO group (RG) with 42 cases each by random number table. Inclusion criteria: ① meet the diagnostic criteria for idiopathic and thrombotic TP in the Diagnostic and Therapeutic Criteria for Hematology (3rd Edition) (9); ② The age is greater than 18; ② The patient and the family members were informed of the specific contents of the study, and the patient agreed to sign the informed consent form. Exclusion criteria: ①

Table 1. General data.

Group(n)	Gender		Age (years)	Course of disease (years)	Types	
	Male	Female			Idiopathic	Thrombotic
NG (42)	20	22	33.48±6.36	3.90±1.45	23	19
RG (42)	19	23	35.24±6.45	3.71±1.40	25	17
χ^2/t	0.048		-1.261	0.613	0.194	
P	0.827		0.211	0.541	0.659	

patients with recurrent TP; ② Patients with acute myelocytic leukemia, cachexia and renal failure; ③ Malignant tumor, cirrhosis ascites, intracranial hemorrhage and other diseases that seriously affect platelet parameters; ④ Those who are allergic to experimental drugs. A total of 84 cases were included in this study. No patients were falling off or interrupted follow-up. The research content is in line with the Helsinki Declaration and was only approved by the Medical Ethics Committee. There was no statistically significant difference in general data between the two groups (P>0.05) (Table 1).

Treatment

NG

Routine treatment is adopted. According to the patient's TP type, carry out the corresponding routine treatment. (I) Idiopathic TP: refer to the Consensus of Experts on Diagnosis and Treatment of Adult Idiopathic TP (10), first, check the platelet parameters of the patient. When the platelet count (PLT) is less than 20×10^9/L, the medical staff instructs the patient to lie down and rest to reduce the possible risk of injury or trauma. If the patient has an obvious bleeding tendency, provide platelet component infusion for the patient. At the same time, prednisone acetate was used. The drug is produced by Rongsheng Pharmaceutical Co., Ltd. of the National Pharmaceutical Group, with the national drug approval number H41020636, the specification is 5mg, the daily dosage is 1.0~1.5mg/kg, and the drug is taken once a day. Check PLT once a week. When PLT returns to normal or approaches normal, gradually reduce the dosage of prednisone acetate, and use a small dose of 5~10mg/d to maintain treatment for 3~6 months. (II) Thrombotic TP: Refer to BCSH: Guidelines for Thrombotic TP and Other Thrombotic Microvascular Diseases for routine treatment (11). The first choice of plasma exchange therapy is to use fresh and frozen plasma to infuse 2000~3000ml twice a day. When the symptoms are relieved and PLT returns to normal, continue infusion for 2 days and gradually increase the plasma exchange interval until it is completely terminated. Some patients were treated with fresh plasma infusion without plasma exchange conditions, and the volume of plasma infusion was 20~40ml/kg per day. At the same time, all patients with thrombotic TP were treated with methylprednisolone succinate, produced by Tianjin Tianyao Pharmaceutical Co., Ltd., with the national drug approval number of H20010097, the applied dose of 80~120 mg/d with intravenous infusion. When PLT>50×10^9/L, the drug gradually transited to oral prednisone treatment, and the dosage was 1-2 mg·kg^{-1}·d^{-1}, and gradually decreased to stop.

RG

Applying rhTPO injection on the basis of routine treat-ment. rhTPO is produced by China Shenyang Sansheng Pharmaceutical Co., Ltd., with national drug approval number S20050049 and a specification of 7500U/1ml. Performing rhTPO subcutaneous injection within 6~24 hours after the completion of routine treatment. The injection dose is set at 300U/kg, once a day, and lasts for 14 days. When the patient's PLT is greater than 50×10^9/L, it is necessary to adjust the frequency of administration to once in 48h, and PLT measurement once a week. When PLT>100×10^9/L or PLT increase more than 50×10^9/L, stop using rhTPO injection. After one course of treatment, that is, 14 days later, the routine treatment of the routine group was carried out.

Observation indicators

Levels of interleukin-2 and interleukin-4

5mL elbow vein blood was drawn from the patients in both groups before and 2 weeks after treatment. After anticoagulation treatment, centrifugal treatment is carried out, and Siemens automatic biochemical analyzer is used. Interleukin 2 (IL-2) and interleukin 4 (IL-4) were determined by double antibody sandwich enzyme-linked immunosorbent assay. After the measurement, the levels of IL-2, IL-4 and IL-2/IL-4 were counted respectively. The kit was produced by eBioscience, and the standard operation was carried out in strict accordance with the instructions of the reagent during the experiment. For ensuring the authenticity of the study data, the tester was completed by the same inspector, who was unaware of the source of the study samples.

Platelet parameters

The mean platelet volume (MPV), platelet specific volume (PCT) and platelet distribution width (PDW) of the blood samples of the two groups at the same period of IL-2 and IL-4 were examined. Platelet count (PLT) was evaluated before treatment, 1 week after, and 2 weeks after treatment according to the actual clinical needs. The automatic blood analyzer produced by Japan East Asia Company was used to detect the platelet parameters.

Indexes of immune function

Before and after the treatment, 3mL of peripheral venous blood was drawn from both groups of patients at fasting in the morning. After centrifugation, blood samples were tested for immune function indicators by flow cytometry. The measurement indicators include CD3+$^+$ and CD4+$^+$. These two indicators are the surface markers of T cells in the immune system. For patients in the treatment and recovery period, the higher the content of these two indicators, the better the recovery and reconstruction of the immune system at the corresponding time. This is an important evaluation index for TP.

The taken time for the patient's platelets to recover to a specific level and the bleeding symptoms to disappear

According to the relevant definitions, take the platelet count of $30 \times 10^9 \cdot L^{-1}$ as a specific standard, and count the time when the platelet count of the two groups of patients rose to the standard. It is generally believed that when the platelet count of the patient rises to this standard, the TP symptoms of the patient have significantly improved. In addition, it also counts the time taken for the bleeding symptoms of patients to disappear. These two indicators can most intuitively reflect the efficacy of different methods from the perspective of patients' recovery.

Treatment effectiveness and adverse reactions

The treatment effectiveness rate reflects the treatment effect of a treatment in a large number of samples from a statistical point of view. For TP, when the platelet count reaches $100 \times 10^9 \cdot L^{-1}$ and above, the treatment method is considered to be effective. At this time, the patient's condition has greatly improved. When the platelet count is below $100 \times 10^9 \cdot L^{-1}$ and above $50 \times 10^9 \cdot L^{-1}$, the treatment method is considered effective, and the patient's bleeding is significantly reduced. If the condition does not improve, it will be judged as invalid. The total effective rate is the percentage of the total effective rate and effective rate in all samples. The main adverse reactions of the treatment used include nausea and local skin redness, so these two symptoms are used as the basis for determining the occurrence of adverse reactions.

Statistical methods

SPSS 25.0 software is used for statistical analysis. The measurement data that conforms to the normal distribution and meets the homogeneity of variance is described by x±s, among which the independent sample t-test is used for inter-group comparison, the paired sample t-test is used for intra-group comparison at different time points, and the count data is described by case number or constituent ratio, and the comparison is χ^2 Inspection. $P<0.05$ means statistically significant.

Results

IL-2 level between two groups of patients

The level of IL-2 in the two groups decreased after treatment compared with that before, but the level in the RG was lower than that in the NGp after treatment $(P<0.05)$ (Table 2).

IL-4 level in two groups of patients

The IL-4 level of patients in both groups decreased after treatment compared with that before treatment, but the level of patients in RG was higher than that in the NG after treatment$(P<0.05)$ (Table 3).

IL2/IL4 level in two groups of patients

The IL2/IL4 indexes of the two groups of patients before and after treatment have changed significantly. Through inter-group comparison, the level of IL-2/IL-4 in RG after treatment was significantly lower than that in the NG $(P<0.05)$ (Table 4). After the statistical results of IL2/IL4 indicators are imaged, the changes in indicators in the two groups can be compared more intuitively. After treatment, the column chart of RG was significantly lower than that of NG. (Figure 1)

Comparison of platelet parameters

The levels of PLT and PCT in the two groups after treatment were higher than those before treatment, but the levels of PLT and PCT in RG patients after treatment were higher than those in NG $(P<0.05)$. The levels of PDW and MPV in the two groups decreased after treatment compared with those before treatment, but the levels of PDW and MPV in RG patients were lower than in NG after treatment $(P<0.05)$ (Table 5).

PLT change trend

Figure 2 shows that the PLT of RG patients 7 days after treatment is $(69.57\pm6.73)\times10^9/L$, higher than NG $(62.05\pm8.52)\times10^9/L$ $(P<0.05)$.

Immune function in two groups of patients

Under the two treatment methods, the CD3+ and CD4+$^+$ of NG and RG patients increased. There was no significant difference between the two groups before treatment, but the CD3+ and CD4+$^+$ of RG were significantly higher than NG after treatment (Table 6).

A comprehensive evaluation of the curative effect

The experiment counted the time it took for the platelet count of NG and RG patients to rise to a specific level and
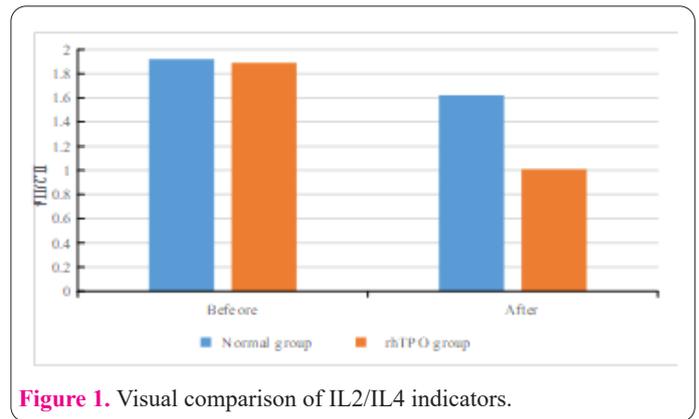

Figure 1. Visual comparison of IL2/IL4 indicators.

Table 2. IL-2 level changes (U/ml, x̄±s).

Groups (n)	Before	After	t	P
NG (42)	21.70±3.39	3.73±0.61	-33.219	<0.001
RG (42)	21.31±3.81	3.05±0.40	-30.847	<0.001
t	0.496	6.464	/	/
P	0.621	<0.001	/	/

Table 3. Changes of IL-4 level (U/ml, x̄±s).

Groups (n)	Before	After	t	P
NG (42)	11.29±2.62	2.30±0.54	-21.914	<0.001
RG (42)	11.25±2.50	3.01±0.58	-22.154	<0.001
t	0.075	-5.776	/	/
P	0.941	<0.001	/	/

Table 4. Comparison of IL-2/IL-4 index (U/ml, x̄±s).

Groups (n)	Before	After	t	P
NG (42)	1.92±0.33	1.62±0.41	-7.48	<0.001
RG (42)	1.89±0.38	1.01±0.27	-5.13	<0.001
t	0.378	5.115	/	/
P	0.621	<0.001	/	/

Table 5. Platelet parameters between the two groups (x̄±s).

Groups (n)	Time	PLT(×10⁹/L)	PDW(%)	PCT(%)	MPV(fl)
NG (42)	Before	36.66±5.35	16.89±2.02	0.08±0.04	13.58±2.74
	After	82.08±15.26	14.14±2.19	0.17±0.04	10.70±1.93
RG (42)	Before	37.04±5.07	16.74±2.43	0.07±0.04	13.63±2.80
	After	96.74±11.06	10.77±1.73	0.21±0.06	8.19±2.00
t_0	/	-0.336	0.303	1.352	-0.076
P_0	/	0.738	0.763	0.180	0.939
t_1	/	-5.041	7.852	-3.791	5.847
P_1	/	<0.001	<0.001	<0.001	<0.001
t_2	/	19.306	-8.766	11.443	-11.781
P_2	/	<0.001	<0.001	<0.001	<0.001
t_3	/	34.904	-10.842	13.747	-10.583
P_3	/	<0.001	<0.001	<0.001	<0.001

Note: t0/P0 is the data comparison between the two groups before treatment. T1/P1 is the data comparison between the two groups after treatment. T2/P2 is the data comparison before and after NG treatment. T3/P3 is the data comparison before and after RG treatment.

Table 6. Changes of immune function indexes (x̄±s).

Groups	CD3+⁺		CD4+⁺	
	Before	After	Before	After
NG (42)	48.27±0.24	59.13±2.84	21.48±1.14	29.89±1.77
RG (42)	48.29±0.31	69.14±3.53	21.11±1.08	39.47±3.31
t	0.214	18.313	0.345	22.371
p	0.398	<0.001	0.514	<0.001

Table 7. Recovery time under two treatments.

Groups	Time taken for platelet count to rise to a specific standard	Time of disappearance of bleeding symptoms
NG (42)	9.58±3.04*	11.45±3.87*
RG (42)	6.85±1.45	8.93±1.15

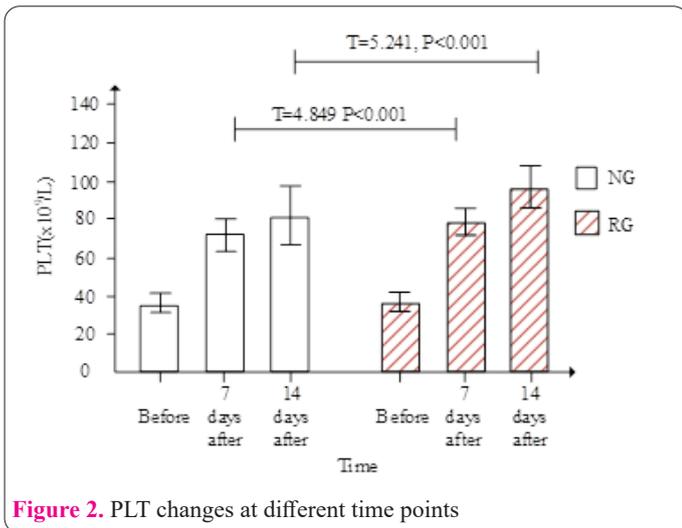Note: * represents a significant difference between this item and RG (P<0.05).

Figure 2. PLT changes at different time points

Table 8. Effective rate and adverse reactions of treatment (n, %).

Indicators	NG (42)	RG (42)
Significant effect (n)	15	23
Effect (n)	17	16
Non-effect (n)	10	3
Total efficiency (%)	76.19	92.86
Vomiting (n)	1	1
Skin redness and swelling (n)	2	1
Total adverse reaction rate (%)	7.14	4.76

the time it took for the bleeding symptoms to disappear. RG consumes less time than NG under both recovery indicators (Table 7).

The comprehensive evaluation of the curative effect also needs to be described from the effective rate and adverse reactions of the treatment. The effective number of rhPTO group was significantly higher than that of NG, and the total effective rate was also higher. There was no significant difference in adverse reactions (Table 8).

Discussion

TP is an acquired disease, which belongs to platelet abnormality syndrome. It is mediated by the patient's own body immunity. The clinical manifestations of TP are various bleeding symptoms, and the platelet content in peripheral blood will be significantly reduced. The disease will seriously reduce the health status and quality of life of patients, and even endanger life in serious cases. With the continuous development of national medical laboratory technology, the disease detection rate of TP has increased year by year (12,13). The occurrence of TP is mainly affected by the destruction and reduction of platelet production and is also an indispensable and important target in clinical practice. Glucocorticoid is one of the main therapies

for various types of TP. As a first-line therapeutic drug, glucocorticoid mainly aims to stimulate platelet proliferation and increase the concentration of fibrinogen. However, this treatment will inhibit the function of neutrophils, leading to an increase in related adverse reactions. Glucocorticoids may cause hypertension, osteoporosis and other symptoms while promoting platelet production. In addition, nausea and vomiting, local skin redness and swelling are also common adverse reactions. Plasma exchange therapy is another TP treatment. This treatment is mostly used in patients with thrombotic TP, which can rapidly improve the platelet content in the body, and is suitable for patients with dangerous conditions, and helps to improve the survival rate. However, plasma exchange requires a lot of economic costs, and glucocorticoid treatment is required at the same time. At present, the first choice of TP treatment is still glucocorticoid, which is combined with plasma exchange and platelet transfusion when necessary. The current TP treatment system is affected by the adverse reactions of the above treatment methods. It brings extremely high economic costs to patients with severe illnesses. Under the influence of these aspects, it is necessary to further explore the treatment methods that can help to recover the platelet content in the body faster.

rhTPO is an artificial recombinant thrombopoietin, which is an exogenous cytokine. As a cytokine closely related to platelet production, thrombopoietin is applicable to all stages of megakaryocyte growth and can produce the effect of promoting platelet production (14). The study found that the decrease of thrombopoietin content in ITP patients was correlated with the decrease of platelet count, and was closely related to the function of T cells (8,15). Zhou et al. (16) combined rhTPO with glucocorticoids in patients with immune thrombocytopenia and found that rhTPO combined with glucocorticoid therapy was able to enhance the overall efficiency of conventional therapy (95.56% vs 76.19%) and produce a promotive effect on PLT and T lymphocytes 1 day after treatment, and had no significant effect on coagulation function. RhTPO is not only suitable for patients with atopic TP and immune TP.

In terms of IL-2 and IL-4, the levels of IL-2 and IL-4 in the two groups of patients after treatment decreased compared with those before treatment, but the level of IL-2 in RG patients after treatment was lower than NG, and the level of IL-4 in RG patients after treatment was higher than NG, the difference was statistically significant ($P<0.05$). therefore, rhTPO treatment on the basis of conventional treatment can more effectively inhibit the level of IL-2 and improve the level of IL-4. According to the results of the IL-2/IL-4 index comparison, the average index values of NG and rhTOP groups before treatment were 1.92 and 1.89 respectively, with no significant difference. After treatment, the IL-2/IL-4 index value of RG was significantly lower than that of NG, which again proved the effectiveness of rhTPO treatment based on conventional therapy. Most scholars agree that rhTPO has immunomodulatory effects, especially on the number of regulatory T cells in the spleen microenvironment (17). Scholars believe that the expression of Th1 and Th2 is highly correlated with the hormone resistance of TP. Therefore, by changing the balance between the two, the expression of T cells can be improved, thus interfering with the symptoms of TP patients. In addition, relevant studies believe that rhTPO can improve the therapeutic effect of TP by improving the

levels of IL-2 and IL-4. T cells mainly secrete a variety of cytokines, especially Th1 represented by IL-2 and the Th2 cell subgroup represented by IL-4 are the dominant factors. From the previous data, the Th1 cell shift phenomenon mainly exists in TP patients (18). After inhibiting IL-2 and increasing IL-4, it can promote the T-cell secretion factor of TP patients to shift towards Th2 and improve the immune imbalance. Therefore, rhTPO treatment can effectively improve the immune imbalance of patients with TP.

Compared with healthy subjects, TP patients were detected to have low hemoglobin and PLT, and high total white blood cell count. Among patients with TP, the platelet count of first-episode patients is extremely low. Other platelet parameters, including mean MPV, platelet density, platelet large cell ratio (P-LCR) and PDW, will also change (19). In this study, compared with the two groups of patients, the levels of PLT and PCT were higher, and the levels of PDW and MPV were lower when rhTPO was used on the 14th day of treatment. The application of rhTPO on the basis of conventional treatment can improve the level of PLT and PCT faster. It is believed that rhTPO can improve platelet count, reduce bleeding risk and reduce platelet transfusion rate, which may improve the safety of invasive surgery and improve the overall survival rate of patients with chronic liver disease (20). In previous studies, it was found that patients treated with rhTPO had a higher platelet recovery rate at 7 days after the operation, and their bleeding score decreased faster, reducing the clinical need for transfusion of a small amount of red blood cells, which was similar to the results of this study (21). Compared with glucocorticoid treatment, rhTPO treatment can recover the PLT level of patients faster, and patients can fully tolerate it, with high safety (22). RhTPO is a platelet-promoting substance obtained based on gene recombination. The principle of this substance to increase the platelet content in patients' blood is to stimulate the division and proliferation of bone marrow megakaryocytes so that it can release more platelets. From the treatment results of the study, the samples treated with rhTPO did have a faster platelet recovery rate.

According to the results of the immune function change test, the CD3+ and CD4+ of NG were 48.27 and 21.48 respectively before treatment and rose to 59.13 and 29.89 respectively after treatment. The CD3+ and CD4+ of RG increased from 48.29 and 21.11 to 69.14 and 39.47. The two immune function indexes of RG were significantly higher than those of NG. The abnormal decline of CD3+ and CD4+ is one of the judgment indicators of TP because immune diseases can cause the decline of these two indicators. For TP, the increase of CD3+ and CD4+ represents the gradual normalization of the patient's immune function, which is one of the important indicators to judge the effect of different methods on TP. In this experiment, the index of RG is much higher than NG, which indicates that rhTPO can effectively improve the patient's condition.

The decrease of platelet content in blood and multiple bleeding symptoms are the most direct clinical manifestations of TP, and also the main factors that threaten the life safety of patients. Therefore, the evaluation of the clinical application effect of rhTPO also needs to start with the recovery time of these two symptoms. According to the experimental results, the platelet count of RG patients recovered to the preset standard for an average of 6.85 days. The average time of NG patients was 9.58 days. Accordin-

gly, the bleeding symptoms of RG patients disappeared for 8.93 days, while the NG value was 11.45 days. The results showed the intervention effect of rhTPO on the condition of patients with TP and the promotion effect of rhTPO on platelet production from a macro perspective. From the perspective of treatment effectiveness, the treatment effective rate of RG reached 92, while that of NG was 76%. The adverse reaction rate of NG was 7.14%, while the value of RG was 4.76%. The difference between the two groups is only 2.38%, with only one case in terms of quantity, so it can be considered that there is no significant difference in the adverse reactions between the two groups.

Because there are many types of TP, this study only observed idiopathic and thrombotic TP as typical samples, and it is still uncertain whether the conclusions of this study can be applied to patients with secondary TP. In the future, the research group will further expand the application of rhTPO to other types of patients with TP, and provide help to verify the effectiveness of rhTPO treatment for different types of TP.

On the basis of conventional therapy, the use of recombinant human thrombopoietin in patients with TP can maintain the balance of T cell activation and inhibition homeostasis, regulate IL-2, IL-4 and platelet parameters, and promote faster recovery of platelet parameters. According to the experimental results, adding rhTPO can accelerate the process of platelet count increase in TP patients and shorten the time required for patients to stop bleeding symptoms.

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