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*Original Article*

# Effect of Stanozolol combined with Cyclosporine A on aplastic anemia

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**Abstract:** Objective: To investigate the clinical efficacy of Stanozolol combined with Cyclosporine A for treatment of aplastic anemia and its influence on cytokine levels. Methods: This is a retrospective analysis of 90 patients with aplastic anemia treated in Department of Hematology, Shandong Provincial Third Hospital from July 2019 to July 2022. According to the different treatment methods, these patients were assigned into a control group and an observation group, with 45 cases in each group. Patients in the control group were treated with Stanozolol alone, while those in the observation group were treated with the combination of Stanozolol and Cyclosporine A. Patients in both groups were treated for six months continuously. The indicators in terms of therapeutic effect, drug onset time, cytokine levels, quality of life, and adverse reactions were recorded and compared between the two groups. Results: After treatment, the total response rate in the observation group was significantly higher than in the control group (91.11% vs. 71.11%, $P<0.05$). The drug onset time in the observation group was shorter than that in control group (42.35±3.68 vs. 68.72±5.49, $P<0.05$). In contrast to the control group, the observation group exhibited significantly decreased levels of tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), and interleukin-2 (IL-2), and an increased level of vascular endothelial growth factor (VEGF) after treatment, with significant differences (all $P<0.05$). The QLQ-C30 scores in the observation group were significantly higher than that in the control group ($P<0.05$). Moreover, there was no statistical difference in the overall incidence of adverse reactions between the two groups (11.11% vs. 17.78%). Conclusion: Stanozolol combined with Cyclosporine A is more effective than Stanozolol alone in treatment of aplastic anemia.

**Keywords:** Stanozolol, Cyclosporine A, aplastic anemia, clinical efficacy

## Introduction

Aplastic anemia is an immune-mediated hematopoietic disorder, which is characterized by pancytopenia and a hypocellular bone marrow and associated with significant mortality [1]. The symptoms of aplastic anemia include easy bleeding or bruising, fatigue, and infections. The majority of acquired aplastic anemia is recognized as idiopathic, and it may be associated with occupational or environmental toxins. According to an epidemiological survey, the estimated annual incidence of aplastic anemia is about two cases per million in western countries, while there is a two/three fold higher incidence in East Asia [2]. A previous study reported that the incidence of aplastic anemia in China was 1.4 per million with severe aplastic anemia and 6.0 per million with non-severe aplastic anemia [3]. Many studies agree that the aims of aplastic anemia treatment are to manage symptoms associated with thrombocytopenia, anemia, to prevent serious hemorrhage and infection through transfusion and other supportive care measures, and to restore hematopoiesis with immunosuppressive therapy and hematopoietic stem cell transplantation [4, 5]. At present, hematopoietic stem cell transplantation is the optimal treatment option for aplastic anemia. However, finding a donor is very difficult, so this approach is relatively limited. Immunosuppressive treatment has become one of the usual methods. The selection of appropriate immunosuppressive agents for patients with aplastic anemia plays an important role in the recovery of life quality and long-term prognosis [6, 7].

The primary clinical treatment for chronic aplastic anemia is targeting bone marrow suppres-

sion. As a protein anabolic steroid, Stanozolol can promote the synthesis of protein, inhibit its heterogenesis, and alleviate bone marrow suppression [8]. However, the application of Stanozolol alone has no immunosuppressive effect and presents poor efficacy. In order to achieve optimal therapeutic effect, a high dosage is usually given in clinical practice, which can increase the risk of adverse reactions in patients, leading to a decrease in treatment compliance and affecting therapy effectiveness. As a calcineurin inhibitor, Cyclosporine A can selectively inhibit the immune response and prevent rejection reaction [9, 10]. It was speculated that the combination of Cyclosporine A and Stanozolol in the treatment of chronic aplastic anemia could effectively overcome the limitations of Stanozolol alone. So far, there is no effective clinical evidence on this topic [11, 12]. Moreover, there are few reports on the comparison of therapeutic effect between the combination medicines and the single drug treatment for aplastic anemia. In this context, this clinical research was designed to investigate the different efficacy between the combination drugs and Stanozolol alone in patients with chronic aplastic anemia in term of total response rate, onset time of drug, cytokine levels, life quality, and adverse reactions. This study is of significance to provide experimental evidence for developing new strategies for clinical treatment of aplastic anemia.

## Materials and methods

### *Subjects*

This is a retrospective analysis. Patients with aplastic anemia admitted to the hematology department of Shandong Provincial Third Hospital from January 2019 to May 2022 were enrolled in this research. This study was approved by the Ethics Committee of Shandong Provincial Third Hospital (Approval number: No. 2018-076).

Inclusion criteria: (1) patients aged 18-70 years old and met the diagnostic criteria for aplastic anemia [13, 14]; (2) patients did not undergo treatment for aplastic anemia before admission; (3) patients were not allergic to the study drugs; (4) patients with good compliance and complete clinical data.

Exclusion criteria: (1) patients with leukemia, myelodysplastic syndrome, or other hematologic system diseases, which caused symptoms of anemia; (2) patients with serious dysfunction of important organs such as heart, lung, kidney, and brain; (3) patients with cognitive impairment; (4) patients who received Stanozolol or Cyclosporine A before; (5) pregnant and lactating women.

According to the inclusion criteria and exclusion criteria, 90 patients with aplastic anemia were included in this study, and their clinical data were retrospectively analyzed. Based on the treatment methods, these patients were divided into a control group and an observation group, with 45 patients in each group. Patients in the control group were treated with Stanozolol alone, while patients in the observation group were treated with Stanozolol and Cyclosporine A.

### *Treatment methods*

All the included patients underwent symptomatic therapies such as hemostatic treatment, anti-infection therapy, liver protection, and maintenance of electrolyte and acid-base balance. Patients in the control group received Stanozolol (Guangxi Nanning Baihui Pharmaceutical Group Co., Ltd., lot number: H45020728) at an oral dose of 2 mg three times a day, while patients in the observation group were given additional Cyclosporine A (Shanghai Donghai Pharmaceutical Co., Ltd., lot number: H10960122), at an oral dose of 2 mg, twice a day. The length of treatment was six months.

### *Observed indexes*

Treatment response: The therapeutic response of patients in the two groups were evaluated. The evaluation criteria were as follows. Cure: after treatment, clinical symptoms including anemic, infection, and bleeding disappeared, male patients with Hb>120 g/L and female patients with Hb>110 g/L, all patients with PLT>80 × $10^9$/L and WBC>4 × $10^9$/L and, no recurrence within one year. Significant response: clinical symptoms, such as anemia, infection, and bleeding, basically disappeared, with WBC>3.5 × $10^9$/L and increased PLT count in all patients, Hb>120 g/L in male patients and Hb>110 g in female patients. Effective response: clinical symptoms were improved after treatment, Hb levels increased by >30 g/L maintaining for more than 3 months. No effect:

**Table 1.** Comparison of general information between the two groups

| Group | Control group (n=45) | Observation group (n=45) | $t/\chi^2$ | P |
|---|---|---|---|---|
| Male/Female (n) | 25/20 | 27/18 | 0.182 | 0.670 |
| Age (years) | 46.51±2.17 | 48.72±3.08 | 1.511 | 0.135 |
| BMI (kg/m$^2$) | 20.45±1.08 | 20.21±0.96 | 1.738 | 0.086 |
| Course of disease (months) | 13.12±2.25 | 12.32±1.92 | 1.098 | 0.276 |
| Diabetes (n) | 5 | 7 | 0.385 | 0.535 |
| Hypertension (n) | 6 | 7 | 0.090 | 0.764 |
| Hyperlipidemia (n) | 6 | 8 | 0.338 | 0.561 |

Note: BMI: Body mass index.

after treatment, the conditions of patients had been not improved, or even aggravated. The total response rate was calculated based on the following formula: total response rate = (1 - number of patients with no effect/total number of patients) × 100%.

Drug onset time: The medicines were considered to take effect when the percentage of peripheral blood reticulocytes was more than 1%. The onset time in patients was calculated and compared.

Levels of cytokines: The levels of cytokines including tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), interleukin-2 (IL-2) and vascular endothelial growth factor (VEGF) were measured in patients before and after treatment. ELISA Kits (R&D science, USA) were used to examine the levels of these cytokines. The assays were conducted strictly following the operating instructions on the kits.

Quality Life Questionnaire Core 30 (QLQ-C30) scores: The QLQ-C30 scale was used to evaluate quality of life in both groups before and after treatment [15]. There were 30 questions in QLQ-C30 scale, including five aspects, physiological function, cognitive function, role function, social function and emotional function. A lower score suggests worse quality of life.

Incidences of adverse reactions: The adverse reactions included elevation of blood pressure, edema of lower limbs, abnormal liver function, and hair growth. The overall incidence of adverse reactions was evaluated and compared.

*Statistical analysis*

The data collected in this research was analyzed using SPSS software (IBM, USA), version 23.0. Measured data were expressed as mean ± standard deviation (SD). The comparisons between two groups were conducted by independent samples t-test, while the comparisons before and after treatment were performed through paired t-tests. Enumerated data were described in the form of case/percentage [n (%)]. The comparisons between two groups were performed through Chi square tests. $P<0.05$ was considered a significant difference.

## Results

*Comparison of general information*

**Table 1** shows that there were no significant differences regarding sex, age, body mass index, course of disease, and underlying diseases between the control group and the observation group (all $P>0.05$), so they were comparable. During the period of treatment, there were no patients lost to follow-up and no patient withdrew. At the end, there were 45 patients in the control group and 45 patients in the observation group. There were no significant differences in basic information between the two groups.

*Comparison of treatment response*

After treatment, the total response rate in the control group was 71.11% (32/45), with 3 cured cases, 13 cases of significant response, and 16 cases of effective response. The total response rate in the observation group was 91.11% (41/45), with 10 cured cases, 23 cases of significant response, and 8 cases of effective response. A significant difference in treatment response was observed between the two groups ($P=0.015$), as shown in **Table 2**.

*Comparison of drug onset time*

As shown in **Figure 1**, the drug onset time for patients taking Stanozolol alone in the control

**Table 2.** Comparison of treatment response between the control group and the observation group

| Group | Cure (cases) | Significant response (cases) | Effective response (cases) | No effect (cases) | Total response rate (%) |
|---|---|---|---|---|---|
| Control group (n=45) | 3 | 13 | 16 | 13 | 71.11 |
| Observation group (n=45) | 10 | 23 | 8 | 4 | 91.11 |
| $X^2$ | | | | | 5.874 |
| P | | | | | 0.015 |

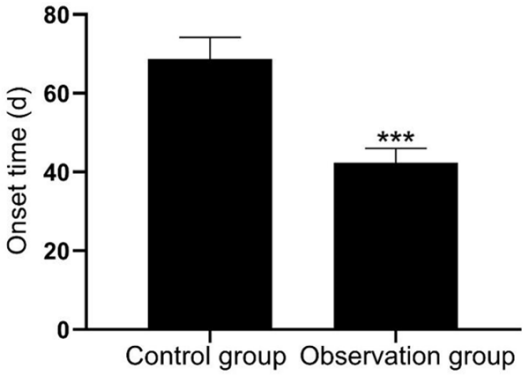


**Figure 1.** Comparison of drug onset time between the control group and the observation group. Compared to the control group, ***P<0.001.

group was 68.72±5.49 d, while the onset time for patients taking Stanozolol and Cyclosporine A in the observation group was 42.35±3.68 d. There was a significant difference in drug onset time between the two groups (P<0.001).

*Comparison of TNF-α, CRP, IL-2, and VEGF levels*

As shown in **Table 3**, there were no significant differences in the serum levels of TNF-α, CRP, IL-2, or VEGF between the control group and the observation group before treatment (P>0.05). At the end of treatment, the TNF-α, CRP, and IL-2 levels were significantly decreased, while the VEGF level was increased in both groups (all P<0.001). In addition, the post-treatment TNF-α, CRP and IL-2 levels were markedly lower while the VEGF level was higher in the observation group than those of the control group, with significant differences (all P<0.001).

*Comparison of QLQ-C30 scores*

Before treatment, QLQ-C30 scores differed insignificantly between the control group and the observation group (57.91±5.18 vs. 58.22±5.69, P>0.05). The QLQ-C30 scores after treatment were significantly higher than those before treatment in both groups (all P<0.001). After treatment, QLQ-C30 scores in the observation group were significantly higher than that in the control group, namely (71.95±6.32 vs. 83.26±6.74, t=11.082, P< 0.001), as shown in **Figure 2**.

*Comparison of adverse reactions*

As shown in **Table 4**, in the control group, there were 1 case with elevation of blood pressure, 1 case with edema of lower limbs, 1 case with abnormal liver function and 2 case with hair growth. In the observation group, there were 2 cases with elevation of blood pressure, 1 case with edema of lower limbs, and 2 cases with abnormal liver function. No statistical difference was observed in incidence of adverse reactions between the two groups.

## Discussion

Aplastic anemia, an unusual hematologic disease, is the paradigm of the human bone marrow failure syndromes, which seriously influences the quality of life, as well as physical and mental health of the patients. The molecular basis of the aberrant immune response and deficiencies in hematopoietic cells has been defined. Immunosuppressive drug therapy is most widely applied approach due to the immediate cost of transplantation, lack of histocompatible sibling donors and so on, and could result in alleviation of pancytopenia, and consequently improvement of hematopoietic function in patients with aplastic anemia [16]. It is confirmed that immunosuppressive treatment is associated with improved clinical outcome [17]. Currently, the first choice of immunosuppressive agents for treatment of aplastic anemia is still investigated.

There are many immunosuppressive drugs for aplastic anemia. Conventional treatment usu-

**Table 3.** Comparison of TNF-α, CRP, IL-2, and VEGF levels between the control group and the observation group

| Group | | Control group | Observation group | t | P |
|---|---|---|---|---|---|
| TNF-α (ng/L) | Before treatment | 26.87±1.94 | 26.91±2.03 | 0.096 | 0.924 |
| | After treatment | 19.56±2.14 | 14.95±1.86 | 10.910 | <0.001 |
| CRP (mg/L) | Before treatment | 56.18±9.57 | 56.42±9.03 | 0.122 | 0.903 |
| | After treatment | 39.25±8.68 | 27.01±5.31 | 8.069 | <0.001 |
| IL-2 (pg/ml) | Before treatment | 11.19±1.15 | 11.02±1.08 | 0.723 | 0.472 |
| | After treatment | 7.06±1.57 | 5.48±1.17 | 5.413 | <0.001 |
| VEGF (ng/L) | Before treatment | 70.42±9.16 | 70.68±10.02 | 0.129 | 0.898 |
| | After treatment | 80.53±9.77 | 110.27±10.54 | 13.880 | <0.001 |

Note: TNF-α: Tumor necrosis factor-α; CRP: C-reactive protein; IL-2: Interleukin-2; VEGF: Vascular endothelial growth factor.

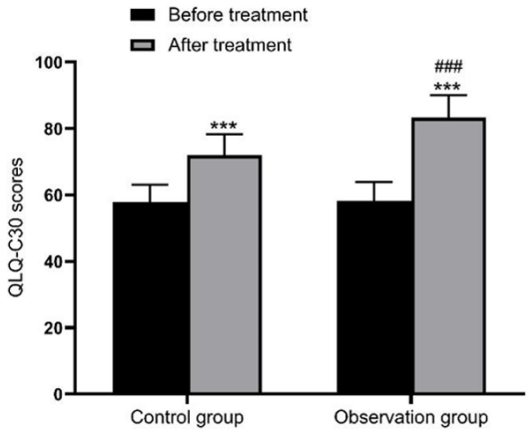


**Figure 2.** Comparison of QLQ-C30 scores between the two groups. Compared to the same group before treatment, ***P<0.001, compared to the control group, ###P<0.001. Note: QLQ-C30: Quality life questionnaire core 30.

ally involves the application of Stanozolol, which is made from protein anabolic hormone and androgens. The mechanism of action of Stanozolol is to enhance 5α and 5β hydroxysteroids levels through the body's metabolism. It acts on the kidney as a target organ, resulting in the increased erythropoiesis. Additionally, it stimulates hepatocyte differentiation and proliferation, effectively enhancing the immune function of the body. Stanozolol also increases the sensitivity of red blood cells to erythropoiesis, accelerating the recovery of hematopoietic function and improving hematopoietic dysfunction in patients. Some studies have indicated a potential role of Stanozolol in stimulating hematopoiesis [18]. It was also reported that Stanozolol could elevate the serum hemopoietin level and increase the level of hemoglobin [19]. The results of this study showed that the total response rate of patients received Stanozolol alone was 71.11%, and the total incidence of adverse reactions reached 11.11%. The above results are similar to those of previous studies [20, 21]. Compared to before treatment, Stanozolol could obviously improve the quality of life of the patients, which is basically in accordance with the results reported before [22]. In addition, another study found that Stanozolol could inhibit T cell immunity [18] and significantly reduce the levels of the serum markers of aplastic anemia in patients with aplastic anemia [5]. In this study, Stanozolol decreased the levels of serum TNF-α, IL-2, and CRP and increased the VEGF level compared to those prior to the treatment.

Although conventional Stanozolol therapy can activate human hematopoietic stem cell telomerase and promote hematopoietic cell proliferation, it is difficult to achieve ideal therapeutic effects using Stanozolol solely. In order to achieve better curative effect, a combined use of drugs was experimented in this research. So far, no statistical conclusion has been drawn on the effects of the combination use of Stanozolol and Cyclosporin A in patients with aplastic anemia in contrast to Stanozolol alone. Cyclosporin A is a powerful immunosuppressive drug, which is a cyclic polypeptide in nature and consists of 11 amino acids. It interacts with substances in the body to produce activating biological complexes. By blocking the activity of neurocalcin, it obstructs information channel conduction and inhibits the synthesis of interleukin-2 and other and reduces interferon and cytokine production in T cells. Cyclosporin A also hampers the synthesis and secretion of negative regulatory factors of

**Table 4.** Comparison of adverse reactions between the control group and the observation group (Cases)

| | Elevation of blood pressure | Edema of lower limbs | Abnormal liver function | Hair growth | Total incidence rate (%) |
|---|---|---|---|---|---|
| Control group (N=45) | 1 | 1 | 1 | 2 | 11.11 |
| Observation group (N=45) | 2 | 1 | 2 | 3 | 17.78 |
| $\chi^2$ | | | | | 0.809 |
| P | | | | | 0.368 |

hematopoietic function, inhibiting their secretion. These mechanisms enhance the body's immune function and mitigate the impact of immune mediation on hematopoietic processes [5]. Many studies showed that Cyclosporin A could treat aplastic anemia through improving bone marrow hematopoietic function [23]. In this study, our results showed that the combination of Stanozolol and Cyclosporin A was more effective than Stanozolol alone in patients with aplastic anemia. This may be because Cyclosporin A, as an immunosuppressive drug, can inhibit the release of inflammatory factors from T lymphocytes by regulating immune function. This action reduces the damage from inflammatory factors on hematopoietic stem cells. Additionally, Cyclosporin A closes the signal transduction pathway of interleukin receptor, thereby improving the immune function of the body and the hematopoietic function of bone marrow. Moreover, in contrast to the control group, the observation group exhibited obviously higher QLQ-C30 scores, shorter onset time, and a higher total response rate, with significant differences. This may be due to the significant efficacy of the combined therapy. Regarding adverse reactions, the results of this study showed that the incidence of adverse reactions in the observation group was higher than that of the control group, but no statistical differences were found between the two groups. This may be associated with the sample size, and it is similar to the results reported by Scheinberg et al. [24]. In addition, immune-mediated damage plays a critical role in development of aplastic anemia. Regulatory T cells can inhibit the differentiation, proliferation, activation, and effector functions of many other types of immune cells. The roles of regulatory T cells in aplastic anemia range from inhibiting T-cell responses to protecting the hematopoietic function of bone marrow. In terms of inflammation, the combined treatment has more advantages, resulting in lower levels of serum TNF-α, and CRP, IL-2 and higher level of serum VEGF. This is because the combination of Stanozolol and Cyclosporin A is able to directly reduce the inflammatory reaction, subsequently improve the vascular endothelial function, increase the peripheral blood count, and finally regulate the bone marrow hematopoietic function. These results are similar to the results reported by Park et al. [24].

In conclusion, the combined use of Stanozolol and Cyclosporin A is more effective than Stanozolol alone in immunological therapy for patients with aplastic anemia, with better treatment response, higher onset time, significant improvement in quality of life, reduced inflammation factors and relatively high safety profile. The results of this research provide experimental basis for clinical treatment of aplastic anemia. However, there are some limitations in this study. The incidence of adverse reactions in the observation group is higher than that in the control group, but there was no statistical difference between the two groups, which may be associated with the small sample size. This is a single-center study, without classification comparison, long-term follow-up results and analysis the related mechanism. Hence, in the future, a large sample size and multicenter controlled long-term follow-up study is needed for further confirmation.

## Disclosure of conflict of interest

None.

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