

Effects of atorvastatin and *Zishen Qingqi granules* on immune function and liver function of patients with systemic lupus erythematosus with mild and moderate activity

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Abstract: To explore the effect of atorvastatin combined with *Zishen Qingqi granules* on the immune function and liver function of patients with mild to moderate activity systemic lupus erythematosus. The data of 120 patients with mild to moderate activity systemic lupus erythematosus admitted to our hospital from February 2019 to February 2020 were retrospectively analyzed and they were divided into experimental group (n=60) and the control group (n=60) according to the order of admission; the control group was treated with atorvastatin, and the experimental group was treated with *Zishen Qingqi granules* plus. The immune function, liver function, TCM syndrome score and systemic lupus erythematosus disease activity index (SLEDAI) were compared between the two groups. The experimental group after treatment was superior to the control group with respect to immune function indexes, liver function indexes, SLEDAI and TCM syndromes (all P<0.001). Atorvastatin combined with *Zishen Qingqi granules* can improve the liver function of patients with mild to moderate activity systemic lupus erythematosus, enhance their immunity, and relieve their clinical symptoms.

Keywords: Atorvastatin, *Zishen Qingqi granules*, systemic lupus erythematosus.

INTRODUCTION

Systemic lupus erythematosus, an autoimmune disease, is characterized by chronic and progressive. Its pathogenic factors include genetics, sex hormones, environmental factors, etc. (Nichilatti *et al.*, 2020). Under the interactive action of multiple factors, the patient's T lymphocytes decrease, the immune function reduces (Shi *et al.*, 2021). Further, the immune complexes formed by the combination of their autoantibodies and the corresponding autoantigens are deposited on the skin, joints, small blood vessels, etc. (Yao *et al.*, 2020; Nishino *et al.*, 2019), causing acute and chronic inflammation and tissue necrosis with the participation of complement. As a result, the patient's multi-organ system is affected. Therefore, improving the patient's immune function and reducing the organ damage is the key to clinical treatment. At present, there is no radical cure for systemic lupus erythematosus in practice. Western medicine mostly uses immuno-suppressive agents, glucocorticoids and plasma exchange as the main treatment methods. Although drugs such as atorvastatin can relieve the disease (Petri, 2020; Kasturi *et al.*, 2020), they produce a negative impact on the liver function of the patient, which is not conducive to the long-term recovery of the patient. In recent years, treatment according to syndrome differentiation and holistic of traditional Chinese medicine has achieved remarkable results in the treatment of chronic diseases. Some scholars have found that *Zishen Qingqi granules*

can improve the level of inflammatory factors in mice with collagen-induced arthritis and enhance their immune function (Wei *et al.*, 2019). The reason is that the drug contains *astragalus*, *Radix Paeoniae Rubra*, raw atractylodes and other drugs. Astragalus polysaccharides can stimulate the proliferation of natural killer cells, and the astragalus water extract can increase the complement content of hepatitis patients and increase the release frequency of immune active substances (Gomes *et al.*, 2021). Additionally, the total glucosides of paeony in *Radix Paeoniae Rubra* are also important drugs for the treatment of autoimmune diseases, hepatitis and other diseases, and can alleviate the clinical symptoms of patients with systemic lupus erythematosus (Xu *et al.*, 2020). Therefore, *Zishen Qingqi granules* may be able to protect the liver of patients, and effectively enhance its immune function.

Currently, the research on the combined application of *Zishen Qingqi granules* and atorvastatin is scarce in the research field. In this regard, we aim to explore the effect of the combination of the two on the immune function and liver function of patients with mild to moderate systemic lupus erythematosus.

MATERIALS AND METHODS

Research design

This study is a retrospective study and was conducted in

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our hospital from February 2019 to February 2020. It aimed to explore the effects of atorvastatin combined with *Zishen Qingqi granules* on the immune function and liver function of patients with mild to moderate activity systemic lupus erythematosus.

Recruitment of subjects

The data of patients with mild to moderate activity systemic lupus erythematosus admitted to the tertiary care or secondary care hospital from February 2019 to February 2020 were retrospectively analyzed. Inclusion criteria: (1) The patient was diagnosed with systemic lupus erythematosus after examination; Western medicine diagnosis met the classification criteria of systemic lupus erythematosus recommended by the American Society of Rheumatology (Solomon-Moore *et al.*, 2019), and the diagnosis of TCM met the relevant standards in the *Guiding Principles for Clinical Research of New Chinese Medicines* (Beqiri *et al.*, 2020); (2) Accord with the systemic lupus erythematosus disease activity index (SLEDAI), the patient's condition was mild (SLEDAI <10 points) or moderate (10 points \leq SLEDAI \leq 14 points); (3) The patient was treated in this hospital for the whole course, without death, transfer to the hospital or stopping treatment; (4) The clinical data of the patient was complete. Exclusion criteria: (1) Unable to communicate with them due to hearing impairment, language impairment, unconsciousness or mental illness; (2) Withdrawal from treatment, death, change of treatment plan or follow-up loss; (3) In pregnancy period or breast-feeding period; (4) Have used hormone therapy recently; (5) Other autoimmune diseases such as multiple myocarditis, rheumatoid arthritis; (6) Complicated with infectious diseases; (7) Drug allergy.

Steps

A total of 120 patients were enrolled in this study, and they were divided into the experimental group (n=60) and the control group (n=60) according to the order of admission. On the day the patients agreed to participate in the study, the study team collected their socio-demographic data and clinical performance data; after analysis, it was found that there was no statistical difference in general information between the two groups of patients (P>0.05), see table 1.

Moral considerations

The study complies with the principles of the Declaration of Helsinki (Hu *et al.*, 2020) and was approved by the review committee of the hospital's ethical review institution (Approved No. of ethic committee: LC2019-01/223). After the patients were recruited, the research team explained to them the purpose, significance, content and confidentiality of the study, and asked them to sign an informed consent form.

Withdrawal criteria

If the following situations occur, patients' data analysis was not performed: (1) adverse events or serious adverse events; (2) illnesses deterioration during the study, etc.; (3) the subject had some serious complications; (4) the subject is unwilling to continue the clinical trial, and requests the research team to withdraw from the clinical trial.

Method

The control group was treated with atorvastatin (Pfizer Pharmaceutical Co., Ltd., SFDA approval no. H20051407), once a day, 10 mg/time, for 12 weeks.

The experimental group was additionally treated with *Zishen Qingqi granules* (Qinhuangdao Runqing Pharmaceutical Co., Ltd., SFDA approval No. B20020516, Specification: 10g/bag), comprising of raw astragalus, *Radix paeoniae alba*, raw atractylodes, raw rehmannia, white oldenlandia diffusa, raw licorice, etc. The patient took it twice a day, 2 bags/time, for a total of 12 weeks.

Observation criteria

(1) General information: The general information including the number of hospitalizations, name, gender, age, body mass, BMI, degree of illness, marital status, education level, income level, payment method of medical expenses, place of residence, lifestyle were compared.

(2) Immune function: The fasting peripheral venous blood was drawn in the morning before and after treatment, and a double-lens immunoturbidity analyzer (Beckman GEM3000, original supporting reagents, Food and Drug Administration, 2008 No. 2401894) No.) were used to determine the patient's immunoglobulin A (IgA), immunoglobulin G (IgG), complement C3, C4 levels.

(3) Liver function: The fasting peripheral venous blood before and after treatment was collected, and a fully automatic biochemical analyzer (Taian Kangyu Medical Instruments Co., Ltd., original supporting reagents, Shandong Food and Drug Administration Standard 2014) No. 2400498) was used to determine alanine aminotransferase (ALT) and γ -glutamyl transpeptidase (γ -GT) levels.

(4) SLEDAI, TCM syndrome scores: The SLEDAI and TCM syndrome scores of patients before and after treatment were compared: SLEDAI (Lim *et al.*, 2019) was scored based on clinical manifestations of the patient's skin, nerves, blood vessels, muscles, joints and other systems, combined with urine routines and blood routines, blood antinuclear antibody and other test results; α TCM syndrome score (Meyer *et al.*, 2020) was scored based on the symptoms of patients with shortness of breath, fatigue, mouth sores, joint muscle pain, general irritability, etc..

STATISTICAL ANALYSIS

The software SPSS 20.0 was used for data analysis, and GraphPad Prism 7 (GraphPad Software, San Diego, USA) for graphics plotting. The research included count data and measurement data, which were examined by X^2 test and t test. Significance was claimed at a P-value of <0.05.

RESULTS

Comparison of general patient data

There was no statistical difference in general information between the two groups ($P>0.05$), see table 1.

Comparison of patient immune function

The immune function indexes of the experimental group after treatment were superior to those of the control group ($P<0.001$), as shown in table 2.

Comparison of patients' liver function

The experimental group witnessed a remarkably better liver function indexes than the control group ($P<0.001$), see table 3.

Comparison of SLEDAI and TCM syndrome scores of patients

Markedly better SLEDAI and TCM syndrome scores of the experimental group after treatment were observed in relative to the control group ($P<0.001$), see table 4.

DISCUSSION

Systemic lupus erythematosus, an autoimmune inflammatory connective tissue disease, is prevalent in young women. The pathogenic factors of the disease are complex. A large number of studies have shown that heredity, environment and estrogen levels are the most important factors affecting its pathogenesis. Under the combined action of these factors, the patient's T lymphocyte content decreases, its inhibitory function decreases, and the massive combination of autoantibodies and antigens activates complement and increases the frequency of inflammatory mediator release, which ultimately leads to inflammation and tissue necrosis. Not only that, the binding of antibodies to cell antigens can cause imbalance in the lymphatic system, causing damage to multiple organs and systems in patients, and seriously affecting their quality of life. At present, western medicine mainly uses immune preparations and other drugs to treat systemic lupus erythematosus. Despite the definite effect, it is easy to cause adverse reactions, and at greater odds of recurrence after stopping the drug (Kumar *et al.*, 2021), thus the application is restricted. With the increasing number of studies on the treatment of systemic lupus erythematosus, some studies have shown that statins can also reduce the disease activity of patients (Seridi *et al.*, 2021). For example, atorvastatin can reduce the total

cholesterol level and low-density lipoprotein level of patients, and inhibit the competition of reductase, protecting the kidney function of patients and preventing them from developing into lupus nephritis. However, the research of scholar Cai X shows that long-term use of atorvastatin can increase the levels of aspartate aminotransferase and alanine aminotransferase in patients with systemic lupus erythematosus (Zhang *et al.*, 2019), indicating that such drugs have an adverse effect on the liver function of patients. The present study did not find that the liver function indexes of the control group decreased after treatment. The reason may be that the patients used atorvastatin for a short time. The effect of atorvastatin on the liver function of patients with systemic lupus erythematosus needs to be further explored. Remarkably, the liver function indexes of the experimental group were significantly better than those of the control group after treatment, which can be attributed to that the astragalus in *Zishen Qingqi granules* has a role in liver and kidney protection. Scholars Fei ZW *et al.* have shown that Astragalus can reduce the level of ET-1 in patients with jaundice, its oxygen free radical scavenging ability is strong, it can down-regulate the expression of ET-mRNA, and then reduce liver damage (Fei *et al.*, 2016).

Notably, Astragalus also has immunomodulatory effects; it can increase the content of white blood cells in the blood; astragalus polysaccharides can regulate the function of T lymphocytes; astragalus water extract can improve the complement content of hepatitis patients, and has a significant promoting effect on the production of antibodies in normal organisms. In addition to astragalus, the total glucosides of paeony contained in white peony also have a concentration and function-dependent two-way immunomodulatory effect on the proliferation or secretion of immune cells. Its positive effect on the immune function of patients with systemic lupus erythematosus has been recognized internationally (Shovman *et al.*, 2018). The current study confirmed that the immune function indexes of the experimental group after treatment were significantly better than those of the control group.

It can be seen that *Zishen Qingqi granules* can yield promising effects in the treatment of systemic lupus erythematosus, but there is no specific name for systemic lupus erythematosus in traditional Chinese medicine, and it is generally classified as *yin* and *yang* poison. Doctors of the past generations have different perceptions of its pathogenesis (Zhao *et al.*, 2019), yet it is mostly believed that the disease is caused by *yin* and *yang* imbalance and *qi*-blood discord. Its pathogenesis is mainly derived from the deficiency of liver and kidney *yin*, and the manifestation is mainly heat toxin congestion. Thus its treatment should be aimed at detoxification and removing blood stasis.

Table 1: Comparison of general information of patients

Groups	Experimental group (n=60)	Control group (n=60)	X ² /t	P
Gender			0.135	0.714
Male	28	26		
Female	32	34		
Age (year)				
Range	20-60	20-56		
average age	38.98±3.65	39.20±3.45	0.339	0.735
Mean weight (kg)	57.58±2.89	57.96±2.10	0.824	0.412
BMI (kg/m ²)	22.54±2.10	22.56±2.23	0.051	0.960
Severity of illness			0.036	0.850
Mild	38	37		
Moderate	22	23		
Medical expenses payment method				
Medical insurance	38	39	0.036	0.849
Business insurance	16	14	0.178	0.673
Others	6	7	0.086	0.769
Marital status			0.147	0.702
Married	38	40		
Single	22	20		
Place of residence			0.034	0.855
City	28	27		
Countryside	32	33		
Monthly income (yuan)			0.035	0.853
≥4000	25	24		
<4000	35	36		
Living habit				
History of smoking	28	26	0.135	0.714
History of drinking	25	24	0.036	0.853
Education background			0.034	0.854
High school and below	26	27		
University and above	34	33		

Table 2: Comparison of immune function of patients (x±s, g/L)

Groups	Experimental group (n=60)	Control group (n=60)	t	P
IgA				
Before treatment	4.23±0.68	4.25±0.67	0.162	0.871
After treatment	1.99±0.20	2.68±0.57	8.848	<0.001
IgG				
Before treatment	18.52±2.51	18.54±2.54	0.043	0.966
After treatment	11.89±1.65	15.23±1.52	11.532	<0.001
C3				
Before treatment	0.68±0.05	0.67±0.05	1.095	0.276
After treatment	1.08±0.13	0.87±0.09	10.288	<0.001
C4				
Before treatment	0.14±0.03	0.13±0.04	1.549	0.124
After treatment	0.25±0.04	0.17±0.03	12.394	<0.001

Table 3: Comparison of liver function of patients (x±s)

Groups	Experimental group (n=60)	Control group (n=60)	t	P
ALT				
Before treatment	260.98±32.68	262.58±34.11	0.262	0.794
After treatment	29.57±3.65	254.64±5.98	248.845	<0.001
γ-GT				
Before treatment	220.68±20.58	221.58±21.50	0.234	0.815
After treatment	92.68±10.26	210.58±12.10	57.566	<0.001

Table 4: Comparison of SLEDAI and TCM syndrome scores of patients (x±s)

Groups	Experimental group (n=60)	Control group (n=60)	t	P
SLEDAI				
Before treatment	13.20±2.65	13.25±2.58	0.105	0.917
After treatment	5.87±0.58	8.65±0.89	20.271	<0.001
TCM syndrome score				
Before treatment	34.58±2.68	34.89±2.14	0.700	0.485
After treatment	11.57±1.50	15.68±1.52	14.908	<0.001

The astragalus in *Zishen Qingqi granules* is a monarch medicine, which can invigorate *qi* and raise *yang*, detoxify and promote muscle growth. *Atractylodes macrocephala*, *Radix Paeoniae Alba* and *Rehmannia glutinosa* are minister medicines, which can remove dampness and cold, cool blood and eliminate blood stasis. The interplay of these plays a role in replenishing *qi* and strengthening the body and relieving the clinical symptoms of patients. Accordingly, the better SLEDAI and TCM syndrome scores of the experimental group after treatment were observed in contrast to the control group.

CONCLUSION

The combination of atorvastatin and *Zishen Qingqi granules* can improve the liver function of patients with mild to moderate activity systemic lupus erythematosus, enhance their immunity and relieve their clinical symptoms.

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