Review Article

Plasmapheresis and Extracorporeal Immunopharmacotherapy in Scleroderma Treatment

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Abstract

Scleroderma or systemic sclerosis is a systemic autoimmune disease with high morbidity and mortality rate. As a result of vasculopathy and fibrosis, there are not only lesions of the skin, but also several internal organs such as lungs, kidneys, and myocardium. Hyperfunction of fibroblasts with increased collagen biosynthesis underlies generalized fibrosis. The main triggers of vascular lesions are elevated levels of anti-endothelial antibodies, circulating immune complexes, signs of T-lymphocyte activation with high levels of cytokines. Drug therapy is often accompanied by complications and is not always able to prevent the progression of the disease. All this determines the indications for plasmapheresis and in severe cases for extracorporeal immunopharmacotherapy when in addition to removing antibodies and other pathological metabolites there is targeted suppression of lymphocytes activity producing antibodies and cytokines.

Keywords: *scleroderma, systemic sclerosis, autoimmune diseases, plasmapheresis, extracorporeal immunopharmacotherapy.*

Introduction

Scleroderma or systemic sclerosis is a systemic autoimmune disease with high morbidity and mortality rate and occurs from 4 to 50 per 100, 000 of the population **(**1-3**)**. This disease is characterized by fibrosis and vasculopathy of the skin and internal organs **(**4**)**. Interstitial pulmonary fibrosis with pulmonary hypertension develops in most patients with scleroderma, significantly aggravates the course of the disease, and is one of the main causes of lethal outcomes **(**5-7**)**. Fibrosis and vasculopathy are the main causes of Raynaud's syndrome development associated with ischemia and ulcers of the terminal phalanges of the fingers **(**8**)**. This is accompanied by ulcerations of the facial skin and mucosa of the oral cavity **(**9**)**. Fibrosis with microcirculation disorders damages both the myocardium and heart valves, accompanied by heart failure, arrhythmias, up to sudden cardiac arrest **(**10**)**. 10-15% of patients develop kidney damage with arterial hypertension, oliguria and thrombotic microangiopathy with a five-year survival rate of up to 50% of patients, despite hemodialysis **(**11**)**. The gullet can also be involved followed by gastroesophageal reflux development **(**12**)**. At the same time, bleeding is possible, both gastrointestinal and pulmonary, cerebral and urogenital **(**13**)**.

Pathogenesis

Hyperfunction of fibroblasts with increased collagen biosynthesis underlies generalized fibrosis. Peripheral Raynaud's syndrome is an early and characteristic sign of scleroderma and has its internal equivalent in the form of visceral (lungs, heart, and kidneys) Raynaud's syndrome. Spasms in combination with microvascular lesions cause macro digital necrosis, pulmonary hypertension, and myocardial ischemia. The target organ is microcirculation with damage to the endothelium, proliferation of intima and smooth muscles, which is accompanied by microangiopathies and microthromboses. The main triggers of vascular lesions are elevated levels of anti-endothelial antibodies of Willebrand factor and factor VIII. Antibodies against annexin-V protein were detected in patients with ischemic finger necrosis **(**14**)**.

The very combination of scleroderma with other systemic autoimmune diseases (polymyositis, lupus erythematosus), along with a high frequency of detection of autoantibodies, circulating immune complexes, signs of T-lymphocyte activation with a high level of cytokines, clearly proves the autoimmune nature and pathogenesis of this disease. The blood plasma of these patients contains antibodies to a wide range of nuclear and cytoplasmic antigens. In addition to lesions of the skin itself, there are antibodies against endothelial cells; this fact determines concomitant vascular pathology associated with increased collagen formation by fibroblasts with perivascular disorders in the early stages of the disease. This determines the significant incidence of scleroderma combined with kidney and myocardium damage.

Treatment

The autoimmune nature of the disease justifies the administration of glucocorticoids, which can reduce the level of autoantibodies and several toxic cytokines (15). However, in addition to well-known complications (Cushing's syndrome, arterial hypertension, diabetes mellitus, osteoporosis), they can promote kidney damage development (16). It is possible to reduce the negative effects of corticosteroids by intravenous administration of immunoglobulins (17). However, such tactics besides their high cost have the danger of transferring viral diseases and allergies. In interstitial lung disease, corticosteroids are combined with cyclophosphamide pulse therapy (18). Mycophenolate mofetil and rituximab are also used (19). However, rituximab can lead to a significant decrease in the diffusion capacity of the lungs (20).

In the case of the kidney damage, angiotensin-converting enzyme inhibitors are used, though, it is not always able to interrupt the progression of kidney failure, requiring hemodialysis and even the kidney transplantation (21). The use of Type V phosphodiesterase inhibitors, endothelin receptor antagonists is also far from being able to stop the progression of the disease, which makes to resort to hematopoietic stem cell transplantation (22, 23). There are attempts to use the photopheresis method when apoptosis occurs during ultraviolet irradiation of lymphocytes and in this form they are returned to circulation (24, 25). In this case, immunosuppression is achieved; however, the accumulated autoantibodies, immune complexes, and other pathological metabolites are not removed.

Apheresis therapy

Insufficient effectiveness and complications of drug therapy suggest the use of efferent therapy, mainly plasmapheresis. With its help, it is possible to remove autoantibodies, immune complexes, cytokines, and other large molecular toxic metabolites from the body (26-28). A good clinical effect was achieved after a course of “programmed” plasmapheresis followed by administration of high doses of immunoglobulins, carried out during the year (29). It was also reported that stable remission was achieved with regular plasmapheresis for 22 years (28). In scleroderma with manifestations of Raynaud's syndrome, plasmapheresis improves hemorheology (rheopheresis), which is especially important for lesions of the fingers (30,31). With predominant damage to the kidneys, especially associated with the development of thrombotic microangiopathy, stabilization of the process can be achieved using plasmapheresis (32-34). Plasmapheresis prevented the progression and interstitial lung disease (35,36).

Extracorporeal Immunopharmacotherapy

A more complete therapeutic effect can be expected with extracorporeal immunopharmacotherapy, being described earlier **(**37**)**. This is achieved by plasmapheresis with the release of lymphocytes, incubating them with a small dose of corticosteroids and their subsequent return to the circulation. In this case, targeted suppression of their activity occurs without toxic effects on the whole body. Reduced levels of autoantibodies, circulating immune complexes and several cytokines (TNF-α, IL-2, INF-γ) with improved clinical symptoms persisted for at least six months.

Our own experience covers the treatment of 23 patients with interstitial lung disease on the background of scleroderma, of which 5 underwent only traditional drug therapy, and 18 – combined with plasmapheresis. At the same time, a more controlled remission was achieved. In particular, over 3 years of observation, the diffusion capacity of the lungs decreased only by 1.83%, while in the control group it decreased by 11.0%. Systolic pressure in the pulmonary artery increased by 2.13% to compare with 4.10% in the control group. A more significant decrease in the content of circulating immune complexes was also observed (in 44.4% of patients versus 20.0% in the control group). Also, one of the patients in the control group died, having increasing pulmonary hypertension.

Conclusion

Thus, scleroderma is an autoimmune disease in which, besides the skin, several vital organs (lungs, kidneys, heart) are affected, which determines the severity of the disease with a high level of morbidity and mortality rate. Drug therapy is not always able to delay the disease progression, especially with the involvement of the internal organs. All this also determines indications for plasmapheresis, with help of which autoantibodies and other pathological metabolites can be removed from the body, considering their molecule size that does not allow them to be excreted by the kidneys. In more severe cases, the use of extracorporeal immunopharmacotherapy with targeted suppression of lymphocyte activity is justified, for they are producers of autoantibodies and toxic cytokines.

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