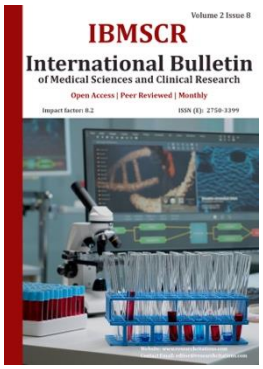

COMPLEX THERAPY OF VASCULAR DISORDERS IN PATIENTS WITH SYSTEMIC SCLERODERMA

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https://doi.org/10.5281/zenodo.13881361

Annotation

Systemic scleroderma (SSc) is a disease in which vascular disorders underlie the pathogenesis and are represented by various clinical manifestations. The article discusses recently published European guidelines for the treatment of this manifestation of SSc.

The importance of the problem of early diagnostics of rheumatic diseases, which began to be actively discussed at the beginning of the 21st century, is beyond doubt. It is especially obvious in relation to systemic scleroderma (SSc), the nosological feature of which is generalized progressive fibrosis, which often determines an unfavorable outcome of the disease. It should be emphasized that, despite the progress of modern pharmacology, the possibilities of effective influence on already developed fibrosis are very limited.

Key words: fibrosis, scleroderma systematica, vascular disorders

Systemic sclerosis (SSc) is a group of systemic connective tissue diseases and is characterized by progressive damage to the skin, musculoskeletal system, internal organs, and generalized vascular damage, which plays a key role in the pathogenesis and clinical picture of SSc and has prognostic significance [1].

Endothelial dysfunction is considered to be the central link in the pathogenesis of Raynaud's syndrome and other vascular disorders. In SSc, the microcirculatory bed is the target of immune-inflammatory damage, leading to disruption of vascular tone, vascular architecture, and blood flow in the affected organs. At the cellular level, endothelial dysfunction is characterized by a change in the phenotype of endothelial cells towards the proinflammatory and proconstrictor component of their metabolism. Raynaud's syndrome, an obligate clinical sign of SSc, is the result of this pathogenetic mechanism. The endothelial hypothesis implies a decrease in the production of vasodilating mediators (prostacyclin, nitric oxide - NO) and an increase in the synthesis of vasoconstrictor agents (endothelin) in the pathogenesis of Raynaud's syndrome. An increase in the level of endothelin in patients with SSD has been identified by many researchers, but a decrease in the concentration of nitrates (which are metabolites of NO) is rarely detected. Along with the deficiency, its excess concentrations were detected in individual patients, which is comparable to the physiological effects of NO - both positive (vasodilating) and negative (tissue-damaging) [2-4].

The main clinical equivalent of microcirculation disorders in SSD is Raynaud's syndrome, characterized by vasospastic crises accompanied by color changes (whitening, redness, cyanosis) and numbness of the fingers, less often the feet, which occur spontaneously or when exposed to cold and excitement.

About half of patients with SSD suffer from trophic disorders at least once during the entire period of the disease, and in 17% they are present constantly - from small ulcers to

severe necrosis and gangrene of the fingers [5]. Tissue ischemia also underlies the development of osteolysis, mainly of the nail phalanges.

The fundamental importance of vascular therapy is obvious, which occupies one of the main places in the complex treatment of the disease. Currently, a wide range of vasoactive drugs is used to treat vascular disorders in SSD. Among them are vasodilators, antiplatelet agents, angioprotectors, including the generally accepted cardiology groups of Ca-blockers, angiotensin-converting enzyme inhibitors and angiotensin II. However, despite the sufficient variety of drugs, scleroderma angiopathy and its severe complications, such as ischemic necrosis and sometimes gangrene, are not always treatable. Even the therapy of Raynaud's syndrome, especially generalized, given its complex pathogenesis and progressive nature, remains a difficult task for practical medicine.

Taking into account a detailed analysis of data from long-term randomized controlled trials by experts from EULAR (European League against Rheumatism) and EUSTAR (EULAR Scleroderma Trials and Research), including with the participation of the Research Institute of Rheumatology, recommendations were proposed for the treatment of SSc, including therapy for digital vasculopathy in scleroderma (Raynaud's syndrome, digital ulcers). A meta-analysis of the effectiveness of dihydropyridine-type calcium antagonists and prostanoids showed that the use of oral nifedipine and infusion iloprost reduces the frequency and severity of Raynaud's syndrome attacks [6, 7]. Calcium entry antagonists, primarily nifedipine, are first-line drugs for the treatment of vascular disorders in SSc, and prostanoids, preferably iloprost, are used to treat severe generalized Raynaud's syndrome with ischemic disorders. Nifedipine is prescribed depending on its tolerability and the severity of Raynaud's syndrome at a dose of 30-60 mg/day for a long time. It has been proven that long-term use of dihydropyridine Ca-blockers significantly reduces the risk of ischemic disorders of the distal extremities [8, 9]. If the effect is insufficient, experts recommend adding infusion prostanoids to the therapy. Iloprost administered intravenously (0.5-3 ng/kg/min for 3-5 days every 6-8 weeks) has demonstrated significant efficacy and advantage over its oral administration. With the combined use of nifedipine and iloprost, adverse vascular events may increase, which requires close monitoring of patients and control of therapy.

Iloprost is a synthetic analogue of prostacyclin, causes suppression of platelet aggregation and activation, dilation of arterioles and venules, increases capillary density and reduces increased vascular permeability caused by mediators such as serotonin and histamine in the microcirculation. It activates endogenous fibrinolysis, exhibits an anti-inflammatory effect, suppresses leukocyte adhesion and migration after endothelial injury, as well as leukocyte accumulation in ischemic tissues.

Randomized controlled trials have shown that infusional prostanoids, mainly iloprost, are effective in healing digital ulcers in patients with SSc [10, 11]. Therefore, iloprost and other available prostanoids should be prescribed to patients with active digital ulcers. In case of insufficient effect of Ca antagonists and especially prostanoid therapy in the presence of multiple digital ulcers in the diffuse form of SSD, EULAR experts recommend the use of bosentan. Bosentan belongs to the group of endothelin receptor antagonists, its effectiveness is based on the effect on endothelial dysfunction, reduction of vasoconstriction, and influence on the process of vascular remodeling. Bosentan is a non-selective endothelin receptor antagonist, prescribed orally at a dose of 62.5 mg 2 times a day for 4 weeks, then 125 mg 2 times a day for 12 weeks [12, 13]. However, despite the existing recommendations, there are

still difficulties in the widespread use of all 3 groups of drugs in the complex therapy of scleroderma vasculopathy (iloprost is not registered in our country, bosentan is not available to most patients due to its high cost). In this regard, the search for available drugs that improve microcirculation and promote healing of digital ulcers in SSD continues. Thus, a pilot study of the tolerability and effectiveness of vasaprostan (prostaglandin E1, alprostadil) was conducted in the clinic of the Research Institute of Rheumatology in patients with severe vascular disorders in various rheumatic diseases. It was found that the inclusion of vasaprostan in the complex treatment of patients with rheumatic diseases with vascular, ischemic and trophic disorders (from digital ulcers to initial gangrene of the extremities) gives a positive effect in 80% of patients. The main group of patients consisted of patients with SSD and with progressive Raynaud's syndrome, as well as individual patients with systemic vasculitis, dermatomyositis and Sjogren's disease in the presence of severe peripheral vascular pathology. Vasaprostan (alprostadil) was administered intravenously by drip in a dose of 20-40 mcg in 250 ml of physiological solution for 2-3 hours every other day or daily. The course included 10-20 infusions. Intra-arterial administration of the drug is also possible [14].

In addition, other drugs have also proven themselves well. The introduction of Actovegin into the therapeutic complex for SSD significantly increases the effectiveness of the treatment of peripheral vascular pathology and the disease as a whole. Actovegin is a deproteinized extract of calf blood, causing activation of the energy metabolism of cells regardless of the organ. The mechanism of action of Actovegin is based on increasing the capture and utilization of glucose and oxygen. These two paired effects improve aerobic energy production in the cell due to the accelerated exchange of adenosine triphosphate and adenosine diphosphate. Clinically, this is manifested by the positive effect of Actovegin in cerebral and peripheral vascular insufficiency [15]. Actovegin effectively affects the processes of cerebral metabolism, has a pronounced effect on peripheral arterial disorders. The clinical effectiveness of the drug in conditions of induced stress and tissue hypoxia in peripheral arterial disorders has been shown. Actovegin stimulates peripheral blood flow, improving peripheral trophism, thereby promoting faster healing of digital ulcers and preventing the occurrence of trophic disorders. Given these properties of Actovegin, we considered it appropriate to use it as an additional therapy for vascular disorders in scleroderma.

It should be emphasized that the therapy of Raynaud's syndrome and trophic disorders is a long-term, multi-year process, often including the complex use of not only drugs from different groups, but also other available treatment methods (hyperbaric oxygenation, reflexo-, psycho-, physiotherapy, digital sympathectomy). The emergence of additional means in the doctor's arsenal to improve microcirculation, reverse development or prevent trophic disorders optimizes therapy, has a positive effect on the quality of life of patients. Taking into account the data obtained, it is advisable to conduct further studies of Actovegin to clarify the effectiveness of its higher doses in Raynaud's syndrome and other localizations of vascular pathology in SSD and other rheumatic diseases. Actovegin can be recommended as a means of additional therapy for vascular disorders in SSD and other rheumatic diseases.

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