Abstract:

The evaluation of vitiligous lesions repigmentation after the administration of 1% simvastatin-acid sodium salt and 1% atorvastatin calcium salt in patients with active vitiligo

Vitiligo is an autoimmune/autoinflammatory skin disease characterized by clearly separated, depigmented patches of various shapes and sizes. Depigmentation can also affect mucous membranes, hair, and the nail apparatus. Depigmentation is the result of dysfunction followed by destruction of melanocytes, which are located in the basal layer of the epidermis and in the hair follicles. The loss of functional melanocytes that characterizes vitiligo has a multifactorial mechanism. The theories explaining the etiology of the disease include genetic, autoimmune, oxidative stress, autoinflammatory, neurogenic factors, adhesion disorders (melanocytorrhagia), but none of the proposed mechanisms seems to be sufficient. Currently, it is believed that vitiligo appears in genetically predisposed individuals, who are affected by various unfavorable external (environmental) and internal factors that induce cell stress in melanocytes, thereby activating autoimmune and autoinflammatory mechanisms.

The treatment of vitiligo is a major challenge in modern dermatology. The current recommendations present many therapeutic approaches including: topical agents (glucocorticoids, calcineurin inhibitors, Janus kinase inhibitors), phototherapy (NB-UVB 311nm, PUVA), systemic glucocorticoids, surgical procedures involving epidermal transplantation, combined methods as well as camouflage or depigmentation treatments. The effectiveness of these methods is still limited. What is more, they are often costly and time-consuming to use.

Statins are commonly used drugs in the treatment of hypercholesterolemia, but according to the contemporary research, a positive effect on the primary and secondary prevention of cardiovascular events may closely correlate with activities beyond the inhibition of cholesterol synthesis. Statins inhibit the proliferation of autoreactive T lymphocytes (CD8+), reduce the production of IFN-γ, increase the production of anti-inflammatory cytokines: IL-4, IL-5 and IL-10, and shift the differentiation of T lymphocytes towards a Th2-dependent response. As a result of their action, a decrease in lymphocyte differentiation towards Th17 cells and an increase in regulatory T-lymphocyte differentiation are also observed. All these activities result in the inhibition of inflammatory processes and lead to obtaining immunotolerance. Statins also cause lymphocyte anergy caused by impaired migration and reduced influx to

inflammatory sites. To date, reports on the use of systemically administered statins in patients with vitiligo indicate their efficacy at the maximum daily doses. Taking into account the pathogenetic aspects of vitiligo and the action profile of statins, an evaluation of the efficacy of these drugs in patients with vitiligo was planned. Due to the high probability of intolerance and possible side effects (especially the risk of developing myopathy or rhabdomyolysis) associated with taking of statins in high daily doses, as well as taking into account the properties of the substances enabling the penetration of particles into the skin, attempt to assess the impact of topically applied statins on vitiligous lesions has been made.

EVRAAS trial was designed as a pilot, single-center, randomized, double-blind, placebo-controlled trial. The active phase of the study was conducted between October and March in order to eliminate the possible influence of solar radiation on the repigmentation of vitiligous lesions. The study population consisted of 24 patients with an active, acrofacial nonsegmental form of vitiligo. The study drugs were ointments containing 1% simvastatin sodium salt acid and 1% atorvastatin calcium salt. The negative control was an ointment containing only the vehicle. The study drugs were applied to the selected upper and lower limb, and the ointment containing the vehicle to the opposing limbs for a period of 12 weeks (twice a day).

The primary endpoint was the assessment of the degree of repigmentation of vitiligous lesions after topical application of 1% atorvastatin calcium salt and 1% simvastatin acid sodium salt in patients with active vitiligo. Secondary endpoints included: percentage of patients who achieved a reduction in absolute area of vitiligo, BSA and VASI scores in the range: 0% none, 1-25% poor, 26-50% moderate, 51-75% good, >75% excellent; comparison of the effectiveness of ointments containing simvastatin and atorvastatin among the studied patients; correlation between the duration of the disease and between the daily use of ointment (estimated in grams per square centimeter of skin surface) and the degree of repigmentation in patients of particular study arms; assessment of the rate of treatment-related adverse events.

Based on the obtained results, it was found that the use of 1% simvastatin acid sodium salt and 1% atorvastatin calcium salt in patients with vitiligo did not allow to achieve significantly better repigmentation than the use of an ointment without active substances. Within the limbs treated with topical simvastatin, inhibition of disease progression was significantly more frequent than in the case of placebo ($p=0.004$), while the difference was not statistically significant for atorvastatin ($p=0.082$).

The EVRAAS study is the first clinical trial in the world to evaluate the effectiveness of topical statin preparations in patients with vitiligo. Taking into account the obtained results and the analysis of the power of the study, more pronounced differences between the assessed variables should be expected in the case of increasing the size of the study groups or extending the active phase of the study.