DOI: https://doi.org/10.17816/dv627134

Review

Angiogenesis in psoriasis as a therapeutic target (literature review)

Nikolay G. Kochergin[1], Anna A. Brezhneva[1], Olga S. Yazkova[2], Alexander A. Fadeev[1]

[1] Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia;

[2] Central polyclinic, Moscow, Russia

ABSTRACT

One of the characteristic features of psoriasis is increased vascularization in the psoriatic plaque. It is known that this process occurs as a result of pathological angiogenesis, which leads to an increase of blood vessels in the lesion, increased proliferation of endothelial cells, vasodilation and increased permeability of the vascular wall, facilitating penetration of immune cells and increasing inflammation. Many signaling molecules are involved in the process of angiogenesis in psoriasis. The most important indicator of the severity of pathological angiogenesis is endothelial vascular growth factor (VEGF). The issue of using blood serum analysis for endothelial vascular growth factor (VEGF) and diagnostic imaging techniques of the vascular network in psoriatic plaques to determine the severity of the process and the possibility of using additional treatment directions aimed at reducing vascularization is being considered. At the moment, the mechanisms of angiogenesis in psoriasis are being actively studied, and the possibilities of therapeutic influence on this link of pathogenesis are especially interesting.

The authors present an analysis of the current literature on this topic, and suggest possible available treatment strategies based on the data obtained. Further research in this direction is needed to optimize the therapy of psoriasis, the main purpose of which will be to reduce the duration of treatment and prolong the time of remission.

Keywords: psoriasis; angiogenesis; endothelial vascular growth factor; VEGF; cryotherapy; PUVA.

To cite this article:

Kochergin NG, Brezhneva AA, Yazkova OS, Fadeev AA. Angiogenesis in psoriasis as a therapeutic target (literature review). *Russian journal of skin and venereal diseases.* 2024;27(3):348–359. DOI: https://doi.org/10.17816/dv627134

Received: 18.02.2024 **Accepted:** 15.04.2024 **Published online:** 04.07.2024

ECO•VECTOR

DOI: https://doi.org/10.17816/dv627134

Научный обзор

Ангиогенез при псориазе как терапевтическая мишень (обзор литературы)

Н.Г. Кочергин[1], А.А. Брежнева[1], О.С. Яцкова[2], А.А. Фадеев[1]

[1] Первый Московский государственный медицинский университет имени И.М. Сеченова (Сеченовский Университет), Москва, Россия;

[2] Центральная поликлиника, Москва, Россия

АННОТАЦИЯ

Одной из характерных особенностей псориаза является повышенная васкуляризация в псориатической бляшке. Известно, что данный процесс происходит в результате патологического ангиогенеза, который ведёт к увеличению кровеносных сосудов в очаге поражения, усилению пролиферации эндотелиальных клеток, вазодилятации и повышенной проницаемости сосудистой стенки, облегчая проникновение иммунных клеток и усиливая воспаление. В процессе ангиогенеза при псориазе задействованы многие сигнальные молекулы. Наиболее важным индикатором выраженности патологического ангиогенеза является эндотелиальный фактор роста сосудов (VEGF). Рассматривается вопрос об использовании анализа сыворотки крови на концентрацию эндотелиального фактора роста сосудов (VEGF) и диагностических методик визуализации сосудистой сети в псориатических бляшках для определения тяжести течения заболевания и разработки дополнительных методов лечения, направленных на снижение васкуляризации. В настоящий момент механизмы ангиогенеза при псориазе активно изучаются, особенно интересны возможности терапевтического влияния на данное звено патогенеза.

Авторами представлен анализ актуальной литературы по данной теме, предложены возможные доступные стратегии лечения с опорой на полученные данные. Показано, что необходимы дальнейшие исследования в этом направлении для оптимизации терапии псориаза, основной целью которой будут сокращение сроков лечения и продление времени ремиссии.

Ключевые слова: вульгарный псориаз; ангиогенез; эндотелиальный фактор роста сосудов; VEGF; общая аэрокриотерапия; ПУВА-терапия.

Как цитировать:
Кочергин Н.Г., Брежнева А.А., Яцкова О.С., Фадеев А.А. Ангиогенез при псориазе как терапевтическая мишень (обзор литературы) // Российский журнал кожных и венерических болезней. 2024. Т. 27, № 3. С. 348–359. DOI: https://doi.org/10.17816/dv627134

Рукопись получена: 18.02.2024 **Рукопись одобрена:** 15.04.2024 **Опубликована online:** 04.07.2024

ЭКО•ВЕКТОР

BACKGROUND

Psoriasis vulgaris is one of the most common chronic recurrent immune-mediated skin diseases with a genetic predisposition, affecting primarily the skin and often the nails and musculoskeletal system. The disease is characterized by hyperproliferation of keratinocytes, impaired keratinization, inflammation, changes in immune regulation, vascular dilation and enhanced angiogenesis. The most characteristic features of psoriasis are infiltrated papules and plaques with desquamation on the surface, changes in nails, and arthropathies [1–3].

Neovascularization is a characteristic feature of psoriasis [4]. There is a tenfold increase in blood flow in psoriatic plaques due to dilation and elongation of papillary capillaries [5]. Some studies demonstrated that angiogenesis precedes the appearance of psoriatic rashes, which disappear when the microcirculatory system is normalized. Angiogenesis facilitates the penetration of the immune cells into the affected area, leads to enlargement of the blood vessels, increased proliferation of the endothelial cells, vasodilation and increased permeability of the vascular wall [6, 7]. Macroscopically, those changes are seen as a well-known Auspitz sign: pinpoint bleeding when scales are removed from the surface of a psoriatic plaque [8].

Vascular endothelial growth factor (VEGF) is the most important indicator of pathological angiogenesis. It mediates angiogenesis and is activated in plaques and blood serum of psoriasis patients. VEGF induces mitogenesis and endothelial cell migration and promotes cell invasion and vascular tube formation. Plasma levels of VEGF type A (VEGF-A) are higher in patients with psoriasis compared to healthy individuals and correlate with the severity of the disease course. Persistently high VEGF levels according to the Psoriasis Area and Severity Index (PASI) criteria even during remission, may be important in determining the time of remission because it promotes vascular permeability, which increases the penetration of inflammatory mediators [9, 10].

One of the main treatment methods in psoriasis is PUVA therapy, the key effect of which is reduction in excessive proliferation of keratinocytes. However, standard treatment of psoriasis is often difficult, and relapses of the disease can occur even after a full course of phototherapy.

New treatment methods aimed at decreasing VEGF and reducing neoangiogenesis may complement standard approaches to treatment of plaque psoriasis and may be useful in treatment of chronic inflammation [8]. It is suggested that general aerocryotherapy in combination with PUVA therapy (long-wave ultraviolet radiation combined with the photosensitizer 8-methoxypsoralen) may have a positive effect on the levels of vascularization in a psoriatic plaque. The effect of aerocryotherapy on VEGF levels which could enhance the effect of PUVA therapy, leading to a more pronounced therapeutic response and longer remission after the main course of treatment is of particular interest.

There are no current literature data on the combined use of PUVA and general aerocryotherapy in treatment of psoriasis. In our opinion, the use of this combination will increase the effectiveness of psoriasis treatment, but the mechanisms of this technology require further investigations.

This review was performed to search for the literature focused on the role of angiogenesis and vascular endothelial growth factor in the development and disease course of psoriasis vulgaris, as well as on the effect of physiotherapeutic methods of PUVA and general aerocryotherapy on these aspects of pathogenesis. For this purpose, we conducted a search using available databases of modern scientific literature and selected relevant articles published in the last 10 years. The studies on the role of angiogenesis and VEGF levels in the pathogenesis of psoriasis vulgaris, as well as the effect of PUVA and aerocryotherapy on the mechanisms of pathological vascularization were analyzed.

ANGIOGENESIS IN PSORIASIS VULGARIS

Vascular changes play a major role in the pathogenesis of psoriasis vulgaris. Characteristic histological features of psoriatic plaques are elongation of interpapillary epidermal wedges, tortuous and dilated capillaries [5]. There is evidence that morphologic changes in the skin, such as dilation and tortuosity of the superficial vascular plexuses, angiogenesis, increased endothelial vein formation, and increased production of alkaline phosphatase in capillaries, may precede visible epidermal hyperplasia in psoriatic plaques [8, 11, 12].

It has been established that the expansion of the vascular network occurs during the development of new blood vessels. Angiogenesis and vasculogenesis are the two mechanisms involved in this process. Angiogenesis occurs when endothelial cells detach from the pre-existing blood vessels, migrate, and proliferate forming the new blood vessels. Vasculogenesis is the de novo formation of blood vessels as a result of differentiation of endothelial progenitor cells [13, 14].

The process of angiogenesis in psoriasis is closely related to the activation of the vascular endothelium by cytokines and growth factors [14]. A.C. Dudley and A.W. Griffioen [15] report that the immune cells producing cytokines such as interleukins (IL) 1, 6, and 22 activate excessive proliferation of keratinocytes. This leads to the expression of VEGF, which activates angiogenesis. VEGF-A in the skin of psoriasis patients is produced mainly by the activated keratinocytes [8].

Angiogenesis involves a large number of stimulating proangiogenic factors produced in psoriatic plaques, such as IL-8, IL-9, IL-17, VEGF, tumor necrosis factor alpha (TNF-α), hypoxia-inducible factor (HIF), fibroblast growth factor (FGF), platelet-derived endothelial cell growth factor (PD-ECGF),

endothelial cell stimulating angiogenesis factor (ESAF), cyclooxygenase-2 (COX-2), vasoactive factors (endothelin and nitric oxide [NO]), and anti-angiogenic factors such as angiostatin, thrombospondin, and endostatin. Disrupted interaction between pro- and anti-angiogenic factors also leads to pathological angiogenesis, which initiates the development of the disease. IL-17 secreted by the Th17 cells upregulates angiogenic factors including VEGF and IL-8. TNF-α produced by the mast cells, macrophages, keratinocytes, and lymphocytes appears to enhance the expression of IL-8, VEGF, FGF, Ang, and Tie-2 receptors in the endothelial cells. These factors have been established to play an important role in the induction of vascular proliferation in psoriatic plaques, as a decrease in their levels is associated with improvement of the skin condition [8, 13, 14].

L. Zhou et al. [12] suggest that the mesenchymal stem cells may be responsible for vascular changes, because the psoriatic mesenchymal stem cells secrete more angiogenic factors such as VEGF and NO and show higher expression levels of angiogenic genes such as HIF1a, transforming growth factor beta (TGF-β), and angiopoietin, compared to normal cells. Mesenchymal stem cells are thought to promote cutaneous capillary proliferation by overexpression of angiogenic cytokines and growth factors. It has been shown that some genes and proteins of dermal mesenchymal stem cells in psoriasis are abnormal and associated with the function of the endothelial cells [16]. In addition, the pathological role of the human dermal microvascular endothelial cells (HDMEC) was reported: in studies in psoriasis patients, they demonstrated increased migration and formation of vascular tubes, as well as decreased proliferation and metabolism, compared to HDMEC in healthy people, which indicated their role in the pathogenesis of psoriasis [17].

Angiogenesis in psoriatic lesions ("inflammatory angiogenesis") is characterized by significant vasodilation, vessel elongation, and increased vascular permeability. In the healthy skin, capillary loops exhibit a predominantly arterial phenotype. In psoriatic plaques, typical features of venous capillaries are present, such as a single or multilayered basal membrane and fenestrated endothelium, including bridging endothelial openings that increase vascular permeability. The role of neoangiogenesis in psoriasis is confirmed by the fact that the improvement of the skin condition with treatment is accompanied by normalization of the new blood vessel formation [8, 13].

Attempts have been made to assess the efficacy of psoriasis treatment by measuring the intensity of microvascular perfusion in plaques, for example, using native capillaroscopic images of the plaque microvessels in psoriasis patients treated with pulsed dye laser [18]. It is suggested that measurement of cutaneous perfusion using non-invasive techniques may be a valuable method to assess the treatment effectiveness. Further studies are needed to investigate whether non-invasive skin imaging can be used to assess residual psoriatic disease activity. S.C. Hanssen et al. [14], who studied the effect of adalimumab on vascularization in psoriasis, reported that non-invasive measurement of vascular function may be a valuable marker of the disease activity. Additional knowledge of the vascular network role and response can be crucial for early assessment of the treatment effectiveness, probably using non-invasive techniques such as Doppler ultrasound skin imaging.

Thus, complex pathologic angiogenesis in a psoriatic plaque additionally increases the influx of proinflammatory cytokines, intensifying the inflammatory process. Active vascularization it noted even before the onset of clinical symptoms and persists even after treatment, possibly playing a role in the rapid relapses of the disease. To date, the influence on the mechanisms of angiogenesis in psoriasis vulgaris are of a great interest.

THE ROLE OF VEGF IN PSORIASIS

The role of VEGF in psoriasis is especially important. It is a typical proangiogenic factor for the Notch input signals, which regulate physiological angiogenesis and neovascularization. It was mentioned before that the levels of many angiogenic factors are increased in psoriasis, but some data indicate that VEGF particularly plays a crucial role in the pathogenesis of psoriasis and neoangiogenesis. VEGF expression has been shown to increase both in the psoriasis foci and in the serum of psoriasis patients. VEGF acts as an autocrine regulator of epidermal hyperplasia, causing keratin imbalance and epidermal hyperplasia in psoriasis, forming the characteristic morphologic lesion [8, 12, 19]. The VEGF family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF), but VEGF-A is believed to be the key regulator of angiogenesis [7, 15].

VEGF promotes the formation of cell adhesion molecules in capillaries and increases vascular permeability, which leads to the migration of leukocytes to the skin, increasing inflammation in psoriasis patients. This process leads to increased oxygen consumption and further activation of other angiogenic factors, making psoriasis difficult to treat. The study of the mechanism of angiogenesis in psoriasis vulgaris showed that the concentration of VEGF-A in patients positively correlated with the PASI (psoriatic lesion area and severity index) and BSA (lesion area index) scores. Thus, VEGF plays an important role in angiogenesis and inflammation and can be used in assessment of the severity of psoriasis [13, 19].

According to different studies, the amount of VEGF in psoriatic plaques is associated with the severity of skin disease, and VEGF plasma levels can predict adverse cardiovascular events in individuals with atherosclerosis. Inhibition of angiogenesis may improve the disease course, while regression of psoriatic plaques may lead to normalization of the microvasculature. Some studies have shown that VEGF deficiency leads to increased endothelial cell apoptosis and blood vessel reduction [12, 17, 20].

Thus, inhibition of angiogenesis by suppression of VEGF may be a promising approach in treatment of psoriasis. This approach is expected to be particularly effective in patients with high levels of VEGF-A. Some patients reported that the use of anti-VEGF agents, such as bevacizumab for cancer treatment, resulted in remission of psoriasis [7, 15].

THE EFFECT OF HYPOXIA AND REACTIVE OXYGEN SPECIES ON ANGIOGENESIS

The additional effects of hypoxia and reactive oxygen species (ROS) on the mechanisms of angiogenesis in psoriasis are currently being studied. In addition to T-cell recruitment, inflammation, abnormal vascular growth, and angiogenesis in the dermis, local hypoxia is observed in psoriasis [21]. There is evidence that hypoxia and inflammation induce the release of various angiogenic factors, which trigger neovascularization. Hypoxia is known to trigger the release of pro-angiogenic factors, namely hypoxia-inducible factor-1 (HIF-1) and cytokines, such as VEGF [16].

VEGF is also regulated by oxygen. The concept of reduced oxygen levels being a central driving force in the formation of a new vascular network was awarded the Nobel Prize in Physiology or Medicine in 2019 [22]. Under low oxygen conditions, signaling pathways induce heterodimerization of the transcription activator HIF-1 associated with adaptation to both cellular and general hypoxia. Since angiogenesis depends not only on the expression of proangiogenic but also antiangiogenic factors, the regulation of angiogenesis depends on the molecular balance between stimulators and inhibitors. Proangiogenic signaling is enhanced by pathophysiological stimuli such as hypoxia, which results from increased tissue mass, vascular dysfunction, and vascular occlusion [8, 15].

A decrease in cellular oxygen levels increases the HIF-1 activity [21]. HIF-1 is a potent VEGF inducer, which is activated by reactive oxygen species and promotes angiogenesis by triggering VEGF expression. Thus, angiogenesis may be induced by ROS-mediated oxidative stress. More and more data indicate that angiogenesis associated with oxidative stress is largely dependent on VEGF [23].

Oxidative stress in psoriasis is a key metabolic factor determining the production of ROS. The Wnt and Notch signaling pathways are also involved in the pathogenesis [24]. Many studies have been conducted to demonstrate the role of oxidative stress in the pathogenesis of psoriasis. It was shown that the expression of the antioxidant superoxide dismutase was decreased in the epidermis and dermis of psoriatic lesions, while the expression of HIF-1α was increased [21].

The increased ROS production occurs if there is antioxidant deficiency, which can be caused by hypoxia. It is now known that ROS-mediated redox signaling plays a central role in angiogenesis. Physiologically ROS play an important role in the cell differentiation and maintenance of homeostasis. Overproduction of ROS (O2 and H2O2), in turn, promotes neovascularization. Proangiogenic factors induce the proinflammatory cells to participate in the pathologic process, which also leads to the formation of ROS. The excess of ROS causes oxidative stress, further stimulating angiogenesis, damaging the cells and tissues and leading to various pathological changes. The expression of cell adhesion molecules and vascular permeability in capillaries increase leading to enhanced leukocyte migration from the skin. This leads to the formation of a pathological circle and the development of chronic skin inflammation characteristic of psoriasis [12, 23].

ROS induce the release of VEGF from various cell types, and VEGF, in turn, promotes endothelial cell migration and proliferation by increasing intracellular ROS. Thus, the VEGF pathway may be a crucial link between oxidative stress, hypoxia, and angiogenesis in psoriasis, especially for the HIF-1α/VEGF signaling pathway, which plays a synergistic role in psoriasis neovascularization. Consequently, the pathway involving hypoxia, ROS, high VEGF levels and consequent enhanced angiogenesis and inflammation may be a potential target for psoriasis treatment. However, the specific relationship between ROS and angiogenesis in psoriasis requires further investigation, which will allow a more complete understanding of the psoriasis pathogenesis and improvement of treatment methods for this disease [23].

TREATMENT METHODS TARGETING PATHOLOGIC ANGIOGENESIS

Monoclonal antibodies to VEGF

The methods that influence the pathologic angiogenesis are considered a new promising direction in treatment of psoriasis vulgaris today. Monoclonal antibodies to VEGF and other antiangiogenic agents are very promising [16]. Therapeutic strategies for VEGF-A blockade have been developed, including (1) direct neutralization of VEGF-A using monoclonal antibodies such as bevacizumab, ranibizumab, and ramucirumab; (2) inhibition of the VEGF-A receptor using VEGF-A receptor tyrosine kinase inhibitors such as sorafenib, regorafenib, sunitinib, and vandetanib; (3) prevention of the VEGF-A binding to its receptors using a false receptor fusion protein that binds to free VEGF-A, such as VEGF Trap (aflibercept). There are reports of improvement in the psoriasis disease course in patients treated with these inhibitors for other conditions and in animal models. It has also been shown that antiangiogenic therapy and a new small-molecule VEGF/VEGFR-2 inhibitor are effective in reducing the number and size of the microvessels in the skin and suppressing angiogenesis in psoriasis [20].

In one study, sunitinib ointment for topical application was demonstrated to supress imiquimod-induced psoriasis-like inflammation by regulating keratinocyte proliferation and apoptosis through suppression of p-Stat3 and VEGF expression [25]. There are also reports that thalidomide is effective in treatment of psoriasis by inhibiting VEGF- and FGF-2-mediated angiogenesis [23].

A pilot study by A. Luengas-Martinez et al. [24] proved the principle for VEGF-A inhibition as an adjuvant treatment strategy to selectively target vascular pathology in psoriasis. It is hypothesized that this approach may be particularly useful in patients with high levels of VEGF-A. It could personalize and complement existing anticytokine strategies and other standard treatments for psoriasis.

Pharmacologic approaches to target the VEGF-A/VEGFR system are now widely used, especially in the fields of oncology and ophthalmology. However, despite the importance of the vascular network in the pathogenesis of psoriasis, no anti-VEGF-A therapy has been approved for treatment [23]. It raises the question of how we can influence neoangiogenesis with physiotherapeutic techniques available in clinical practice.

Antioxidants

It is known that the use of the drugs targeting oxidative stress, such as antioxidants, is highly beneficial in treatment of skin diseases. For example, studies have shown that glabridin suppresses imiquimod-induced psoriasis-like inflammation in the skin of BALB/c mice by improving antioxidant status and reducing the levels of pro-inflammatory cytokines.

Colchicine significantly induces protective response to oxidative stress in neutrophils by reducing lipid peroxidation and modulating Ca2+ release.

More importantly, high doses of vitamin C can also be effective in treatment of skin diseases due to its antioxidant properties. Thus, proanthocyanidins are widely used in treatment of various diseases associated with oxidative stress and angiogenic factors due to their potent antioxidant, anti-angiogenetic, antiproliferative, and anti-oncogenetic properties [23].

PUVA therapy

Despite tremendous advances in psoriasis therapy and the use of numerous highly effective biological drugs, current clinical guidelines still recommend PUVA as first-line therapy for moderate to severe psoriasis. It is known that phototherapy can suppress systemic inflammation in psoriasis patients by reducing serum levels of CRP and IL-6. PUVA acts mainly by suppressing keratinocyte proliferation, inducing apoptosis, regulating the function of lymphocytes and antigen-presenting cells, and reducing the production of cytokines such as TNF-α. In the study by S. Coimbra et al. [9], a significant decrease in VEGF levels was observed at the end of PUVA course, but VEGF plasma levels were still significantly higher than in the control group [26]. It is assumed that PUVA can reduce VEGF expression by primary influence on VEGF production by keratinocytes or by inhibiting keratinocyte proliferation as a secondary effect [27].

PUVA is known to reduce excessive keratinocyte proliferation in psoriasis. However, there is evidence that ultraviolet light can induce ROS that activate the inflammatory pathway via the NF-κB transcription factor (nuclear factor kappa-light-chain-enhancer of activated B cells). The suppression of ROS, resulting in the decreased production of TNF-α and angiopoietin-2, is poorly understood [28].

Phototherapy is highly effective but also causes adverse reactions, which can be significantly reduced by careful patient management and attention to contraindications. The known consequences of high cumulative doses of ultraviolet light are skin photoaging and photocarcinogenesis. An increased risk of squamous cell cancer was described after > 150 PUVA procedures, with a significantly increased risk reported after > 350 procedures. Data from American publications indicate an increased risk of melanoma development after PUVA, but this may be partly due to the fact that American protocols include monthly maintenance procedures after remission is achieved, whereas European protocols do not recommend further irradiation after remission and do not show an increased risk of melanoma development [27].

To optimize psoriasis treatment and reduce the risk of side effects it is necessary to minimize the number of PUVA procedures with achievement of a pronounced clinical effect and long-term remission after a full course of therapy.

General aerocryotherapy

General aerocryotherapy is a method of briefly exposing the human body to extremely low temperatures for medical purposes. As a rule, cooled air, usually in the form of liquid nitrogen, is used. General aerocryotherapy was introduced about 35 years ago, however, it wasn't sufficiently studied in dermatologic patients. For centuries, low temperatures have been used for therapeutic, recreational, and athletic purposes to accelerate recovery. The work of Hippocrates suggested that cold therapy could "relieve fatigue" by reducing depletion of energy or strength; references to the use of ice and snow to treat edema have led some to consider them a precursor to cryotherapy. Exposure to cold is thought to accelerate recovery due to its vasoconstrictive effect which decreases inflammation and metabolism [29–31].

It could be reasonable to study the effects of general aerocryotherapy on previously described mechanisms of angiogenesis, proangiogenic factors, hypoxia and ROS in psoriasis. There is evidence that cryotherapy reduced the levels of inflammatory markers IL-6 and TNF-α in patients with rheumatoid arthritis [32].

Reactive oxygen and nitrogen species play key roles as signaling molecules and vasodilators in the activation

of growth factors such as FGF, VEGF, insulin-like growth factor I (IGF-1), hepatocyte growth factor (HGF), platelet derived growth factor BB (PDGF-BB), and brain-derived neurotrophic factor (BDNF), which are extracellular signals regulating the functions of the muscular, cardiovascular, and nervous systems. According to the literature, general aerocryotherapy significantly reduces the production of ROS and nitric oxide (H2O2 and NO), as well as the concentration of serum IL-1β and C-reactive protein. There is evidence that general aerocryotherapy also reduces the levels of circulating growth factors such as HGF, IGF-1, PDGF-BB, VEGF, and BDNF [33].

The physiologic benefits of general aerocryotherapy are attributed to the suppression of inflammation and cytokine release induced by reactive oxygen and nitrogen species. Cryotherapy also reduces oxidative stress and inflammatory response without remodeling the extracellular matrix. Hydrogen peroxide (H2O2) and nitric oxide (NO) are produced mainly during the inflammatory response [33]. H2O2 and NO molecules are involved in the transcription regulation through redox modification or nitrosation of transcription factors, which induce the expression of many molecules such as cytokines and growth factors. Thus, the immunomodulatory effects of cryotherapy may be useful in chronic autoimmune diseases [32].

Studies in animal models show that moderate hypothermia (with local and/or core body temperature around 30°C) can suppress the leukocyte infiltrate formation, gene transcription of pro-inflammatory cytokines, enzymatic pathways such as collagenases, metalloproteinases, and pro-angiogenic agents such as VEGF. For example, in rheumatoid arthritis, cryotherapy can reduce levels of pro-inflammatory cytokines and proteolytic enzymes. There is evidence that cryotherapy reduced serum TNF-α levels and tended to reduce serum IL-6 levels in 40 patients with rheumatoid arthritis. The molecular pathways targeted by cryotherapy (proinflammatory cytokines, VEGF) suggest some interesting anti-inflammatory properties of cryotherapy in rheumatic inflammatory diseases that require further investigation [26].

H. Tabisz et al. [34] concluded that general aerocryotherapy has the potential to improve performance and reduce the severity of symptoms in some chronic conditions. There was a 4.3-fold decrease in TNF-α levels, and an increase in the anti-inflammatory cytokine IL-10. In addition, the authors of the study made a hypothesis based on the mechanisms of vasoconstriction, supported by an increase in the expression of adrenergic α-receptors, rather than sympathetic nerve activity, while sympathetic activity itself decreases [31].

Some studies report a 29.5% reduction in the blood flow in the superficial skin vascular networks (at a depth of up to 2 mm), while others report a 91% reduction [35, 36]. The study [34] reported a 45% to 74% reduction in the blood flow in the deep vascular networks (at a depth of 8 mm). As a result of local vasoconstriction, the reduction in the blood flow led to a decrease in the temperature of the blood-supplied tissues. The main goal of cryotherapy is heat removal, which is facilitated by a decrease in the cell and tissue core temperature and blood flow [30]. This mechanism may be useful in suppressing pro-inflammatory cytokines and growth factors in inflammatory foci. In the study [30], exposure to general aerocryotherapy was reported to cause a rapid decrease in temperature in the outer layers of human skin, leading to the release of endorphins and a subsequent pain reduction.

General aerocryotherapy is often used in rheumatoid arthritis. There is evidence that cryotherapy can inhibit the regulation of mediators involved in inflammation and joint destruction (cytokines, enzymes, proangiogenic factors). The technique is used in a wide range of rheumatic diseases as a symptomatic treatment due to its analgesic, anti-inflammatory, myorelaxant, vasoconstrictor, enzyme-blocking, and antioxidant effects. Recent studies have shown potential effects of cryotherapy on important molecular and cellular targets involved in immune inflammation, such as pro-inflammatory cytokines, VEGF, enzymatic pathways (metalloproteinases, collagenase), ICAM-1 adhesion molecules, leukocyte infiltrate formation and oxidative stress in rats and humans, and norepinephrine in humans.

By increasing norepinephrine levels cryotherapy can decrease IL-6 and iNOS levels, which are known to be involved in the endothelial dysfunction and inflammation [26]. In addition, there is evidence that general aerocryotherapy has a positive effect on metabolic syndrome and serum lipid levels, which is useful in psoriatic patients with comorbidities. The advantages of the procedure are no medication use, no invasive techniques, and no other specialists involved, except for a physiotherapist [29].

To improve the effectiveness of psoriasis treatment additional suppression of neoangiogenesis with a combination of PUVA and general aerocryotherapy is being considered. This technique supposedly reduces excessive angiogenesis by correcting tissue hypoxia, decreasing ROS levels, and reducing serum VEGF levels [32]. We suggest that the efficacy of PUVA may increase with the additional effect of general aerocryotherapy on pathologic angiogenesis and inflammation. Such a technique is of particular interest due to its availability, good tolerability, and minimal contraindications. Presumably, the combination of PUVA with general aerocryotherapy can increase the remission time due to the normalization of the vascular system.

CONCLUSION

Psoriasis cannot be cured to date due to its complex pathogenesis. The main goal of treatment is to control and stabilize the course of the disease, slow down the progression, reduce clinical symptoms such as erythema,

scaling, plaque infiltration and pruritus, reduce short- and long-term adverse reactions, control psoriasis-related complications, and improve the quality of life.

To date, the studies on the use of general aerocryotherapy in treatment of psoriasis are insufficient. The effects of aerocryotherapy on angiogenesis in patients with psoriasis are of particular interest. It is supposed that combination of PUVA and general aerocryotherapy can improve the clinical effect, prolong remission time, reduce VEGF and ROS levels, increase tissue oxygenation, and decrease proinflammatory cytokines blood levels. Moreover, this treatment is widely available and well tolerated and can be used if there are contraindications to systemic therapy.

Thus, further studies are needed to optimize treatment of psoriasis using available physiotherapeutic techniques.

ADDITIONAL INFORMATION

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. N.G. Kochergin — research concept, making significant edits to the manuscript in order to increase the scientific value of the article; O.S. Yazkova, A.A. Fadeev — editing the article; A.A. Brezhneva — collection and analysis of literature sources, text writing.

REFERENCES

1. Olisova OYu, Kochergin NG, Paramonov AA, et al. Clinical and genetic associations of T-cell receptors repertoire in psoriasis. *Pathogenesis.* 2023;21(2):47–54. EDN: KKGXKB doi: 10.25557/2310-0435.2023.02.47-54

2. Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: A review. *JAMA.* 2020;323(19):1945–1960. doi: 10.1001/jama.2020.4006

3. Kaushik SB, Lebwohl MG. Psoriasis: Which therapy for which patient. Psoriasis comorbidities and preferred systemic agents. *J Am Acad Dermatol.* 2019;80(1):27–40. doi: 10.1016/j.jaad.2018.06.057

4. Rendon A, Schäkel K. Psoriasis pathogenesis and treatment. *Int J Mol Sci.* 2019;20(6):1475. doi: 10.3390/ijms20061475

5. Goldsmith LA, Katz SI, Gilchrist BA, et al. *Fitzpatrick's dermatology in clinical practice.* Trans. from English. Ed. by N.N. Potekaev, A.N. Lvov. 2nd ed. Moscow: Izdatel'stvo Panfilova; 2015. Vol. 1. 1168 p. (In Russ).

6. Ghoreschi K, Balato A, Enerbäck C, Sabat R. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. *Lancet.* 2021;397(10275):754–766. doi: 10.1016/S0140-6736(21)00184-7

7. Luengas-Martinez A, Paus R, Young HS. Antivascular endothelial growth factor-A therapy: A novel personalized treatment approach for psoriasis. *Br J Dermatol.* 2022;186(5):782–791. doi: 10.1111/bjd.20940

8. Lee HJ, Hong YJ, Kim M. Angiogenesis in chronic inflammatory skin disorders. *Int J Mol Sci.* 2021;22(21):12035. doi: 10.3390/ijms222112035

9. Coimbra S, Oliveira H, Reis F, et al. Interleukin (IL)-22, IL-17, IL-23, IL-8, vascular endothelial growth factor and tumour necrosis factor-α levels in patients with psoriasis before, during and after psoralen-ultraviolet A and narrowband ultraviolet B therapy. *Br J Dermatol.* 2010;163(6):1282–1290. doi: 10.1111/j.1365-2133.2010.09992.x

10. Pritulo OA, Petrov AA. Comprehensive assessment of the dynamics of angiogenesis in patients with psoriasis treated with methotrexate. *Vestnik dermatologii i venerologii.* 2023;99(1):37–47. doi: 10.25208/vdv1387

11. Hou H, Li J, Wang J, et al. ITGA9 inhibits proliferation and migration of dermal microvascular endothelial cells in psoriasis. *Clin Cosmet Investig Dermatol.* 2022;15:2795–2806. doi: 10.2147/CCID.S394398

12. Zhou L, Wang J, Liang J, et al. Psoriatic mesenchymal stem cells stimulate the angiogenesis of human umbilical vein endothelial cells in vitro. *Microvasc Res.* 2021;136:104151. doi: 10.1016/j.mvr.2021.104151

13. Socha M, Kicinski P, Feldo M, et al. Assessment of selected angiogenesis markers in the serum of middle-aged male patients with plaque psoriasis. *Dermatol Ther.* 2021;34(1):e14727. doi: 10.1111/dth.14727

14. Hanssen SC, van der Vleuten CJ, van Erp PE, et al. The effect of adalimumab on the vasculature in psoriatic skin lesions. *J Dermatolog Treat.* 2019;30(3):221–226. doi: 10.1080/09546634.2018.1506082

15. Dudley AC, Griffioen AW. Pathological angiogenesis: Mechanisms and therapeutic strategies. *Angiogenesis.* 2023;26(3):313–347. doi: 10.1007/s10456-023-09876-7

16. Han Q, Niu X, Hou R, et al. Dermal mesenchymal stem cells promoted adhesion and migration of endothelial cells by integrin in psoriasis. *Cell Biol Int.* 2021;45(2):358–367. doi: 10.1002/cbin.11492

17. Li J, Hou H, Zhou L, et al. Increased angiogenesis and migration of dermal microvascular endothelial cells from patients with psoriasis. *Exp Dermatol.* 2021;30(7):973–981. doi: 10.1111/exd.14329

18. Hern S, Stanton AW, Mellor RH, et al. In vivo quantification of the structural abnormalities in psoriatic microvessels before and after pulsed dye laser treatment. *Br J Dermatol.* 2005;152(3):505–511. doi: 10.1111/j.1365-2133.2005.06435.x

19. Gong J, Yang H, Qi D, Tang X. The association of serum vascular endothelial growth factor levels and psoriasis vulgaris: A protocol for systematic review and meta-analysis. *Medicine (Baltimore).* 2020;99(33):e21565. doi: 10.1097/MD.0000000000021565

20. Mohta A, Mohta A, Ghiya BC. Assessing the association between psoriasis and cardiovascular ischemia: An investigation of vascular endothelial growth factor, cutaneous angiogenesis, and

arterial stiffness. *Indian Dermatol Online J.* 2023;14(5):653–657. doi: 10.4103/idoj.idoj_246_23

21. Zhu WJ, Li P, Wang L, Xu YC. Hypoxia-inducible factor-1: A potential pharmacological target to manage psoriasis. *Int Immunopharmacol.* 2020;86:106689. doi: 10.1016/j.intimp.2020.106689

22. Griffioen AW, Bischoff J. Oxygen sensing decoded: A Nobel concept in biology. *Angiogenesis.* 2019;22(4):471–472. doi: 10.1007/s10456-019-09692-y

23. Xian D, Song J, Yang L, et al. Emerging roles of redox-mediated angiogenesis and oxidative stress in dermatoses. *Oxid Med Cell Longev.* 2019;2019:2304018. doi: 10.1155/2019/2304018

24. Luengas-Martinez A, Ismail D, Paus R, Young HS. Inhibition of vascular endothelial growth factor-A downregulates angiogenesis in psoriasis: A pilot study. *Skin Health Dis.* 2023;3(5):e245. doi: 10.1002/ski2.245

25. Kuang YH, Lu Y, Liu YK, et al. Topical sunitinib ointment alleviates psoriasis-like inflammation by inhibiting the proliferation and apoptosis of keratinocytes. *Eur J Pharmacol.* 2018;824:57–63. doi: 10.1016/j.ejphar.2018.01.048

26. Guillot X, Tordi N, Mourot L, et al. Cryotherapy in inflammatory rheumatic diseases: A systematic review. *Expert Rev Clin Immunol.* 2014;10(2):281–294. doi: 10.1586/1744666X.2014.870036

27. Kurz B, Berneburg M, Bäumler W, Karrer S. Phototherapy: Theory and practice. *J Dtsch Dermatol Ges.* 2023;21(8):882–897. doi: 10.1111/ddg.15126

28. Chua RA, Arbiser JL. The role of angiogenesis in the pathogenesis of psoriasis. *Autoimmunity.* 2009;42(7):574–579. doi: 10.1080/08916930903002461

29. Olisova OYu, Kayumova LN, Smirnov KV, General cryotherapy with the use of cryocapsule ICEQUEEN in patients with various dermatoses. *Russ J Skin Venereal Dis.* 2017;20(1):15–20. EDN: YGTAIR doi: 10.18821/1560-9588-2017-20-1-15-20

30. Allan R, Malone J, Alexander J, et al. Cold for centuries: A brief history of cryotherapies to improve health, injury and post-exercise recovery. *Eur J Appl Physiol.* 2022;122(5):1153–1162. doi: 10.1007/s00421-022-04915-5

31. Hohenauer E, Costello JT, Deliens T, et al. Partial-body cryotherapy (-135°C) and cold-water immersion (10°C) after muscle damage in females. *Scand J Med Sci Sports.* 2020;30(3):485–495. doi: 10.1111/sms.13593

32. Kujawski S, Newton JL, Morten KJ, Zalewski P. Whole-body cryostimulation application with age: A review. *J Therm Biol.* 2021;96:102861. doi: 10.1016/j.jtherbio.2021.102861

33. Zembron-Lacny A, Morawin B, Wawrzyniak-Gramacka E, et al. Multiple cryotherapy attenuates oxi-inflammatory response following skeletal muscle injury. *Int J Environ Res Public Health.* 2020;17(21):7855. doi: 10.3390/ijerph17217855

34. Tabisz H, Modlinska A, Kujawski S, et al. Whole-body cryotherapy as a treatment for chronic medical conditions? *Br Med Bull.* 2023;146(1):43–72. doi: 10.1093/bmb/ldad007

35. Ho SS, Illgen RL, Meyer RW, et al. Comparison of various icing times in decreasing bone metabolism and blood flow in the knee. *Am J Sports Med.* 1995;23(1):74–76. doi: 10.1177/036354659502300112

36. Knobloch K, Grasemann R, Spies M, Vogt PM. Midportion achilles tendon microcirculation after intermittent combined cryotherapy and compression compared with cryotherapy alone: A randomized trial. *Am J Sports Med.* 2008;36(11):2128–2138. doi: 10.1177/0363546508319313

СПИСОК ЛИТЕРАТУРЫ

1. Олисова О.Ю., Кочергин Н.Г., Парамонов А.А., и др. Клинико-генетические ассоциации репертуара Т-клеточных рецепторов при псориазе // Патогенез. 2023. Т. 21, № 2. С. 47–54. EDN: KKGXKB doi: 10.25557/2310-0435.2023.02.47-54

2. Armstrong A.W., Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: A review // JAMA. 2020. Vol. 323, N 19. P. 1945–1960. doi: 10.1001/jama.2020.4006

3. Kaushik S.B., Lebwohl M.G. Psoriasis: Which therapy for which patient. Psoriasis comorbidities and preferred systemic agents // J Am Acad Dermatol. 2019. Vol. 80, N 1. P. 27–40. doi: 10.1016/j.jaad.2018.06.057

4. Rendon A., Schäkel K. Psoriasis pathogenesis and treatment // Int J Mol Sci. 2019. Vol. 20, N 6. P. 1475. doi: 10.3390/ijms20061475

5. Голдсмит Л.А., Кац С.И., Джилкрест Б.А., и др. *Дерматология Фицпатрика в клинической практике* / пер. с англ.; под общ. ред. Н.Н. Потекаева, А.Н. Львова. Изд. 2-е, исп., перер., доп. Москва: Издательство Панфилова, 2015. Т. 1. 1168 с.

6. Ghoreschi K., Balato A., Enerbäck C., et al. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis // Lancet. 2021. Vol. 397, N 10275. P. 754–766. doi: 10.1016/S0140-6736(21)00184-7

7. Luengas-Martinez A., Paus R., Young H.S. Antivascular endothelial growth factor-A therapy: A novel personalized treatment approach for psoriasis // Br J Dermatol. 2022. Vol. 186, N 5. P. 782–791. doi: 10.1111/bjd.20940

8. Lee H.J., Hong Y.J., Kim M. Angiogenesis in chronic inflammatory skin disorders // Int J Mol Sci. 2021. Vol. 22, N 21. P. 12035. doi: 10.3390/ijms222112035

9. Coimbra S., Oliveira H., Reis F., et al. Interleukin (IL)-22, IL-17, IL-23, IL-8, vascular endothelial growth factor and tumour necrosis factor-α levels in patients with psoriasis before, during and after psoralen-ultraviolet A and narrowband ultraviolet B therapy // Br J Dermatol. 2010. Vol. 163, N 6. P. 1282–1290. doi: 10.1111/j.1365-2133.2010.09992.x

10. Притуло О.А., Петров А.А. Комплексная оценка динамики показателей ангиогенеза у больных псориазом при лечении метотрексатом // Вестник дерматологии и венерологии. 2023. Т. 99, № 1. С. 37–47. EDN: UDFZPY doi: 10.25208/vdv1387

11. Hou H., Li J., Wang J., et al. ITGA9 inhibits proliferation and migration of dermal microvascular endothelial cells in psoriasis // Clin Cosmet Investig Dermatol. 2022. Vol. 15:2795–2806. doi: 10.2147/CCID.S394398

12. Zhou L., Wang J., Liang J., et al. Psoriatic mesenchymal stem cells stimulate the angiogenesis of human umbilical vein endothelial cells in vitro // Microvasc Res. 2021. Vol. 136. P. 104151. doi: 10.1016/j.mvr.2021.104151
13. Socha M., Kicinski P., Feldo M., et al. Assessment of selected angiogenesis markers in the serum of middle-aged male patients with plaque psoriasis // Dermatol Ther. 2021. Vol. 34, N 1. P. e14727. doi: 10.1111/dth.14727
14. Hanssen S.C., van der Vleuten C.J., van Erp P.E., et al. The effect of adalimumab on the vasculature in psoriatic skin lesions // J Dermatolog Treat. 2019. Vol. 30, N 3. P. 221–226. doi: 10.1080/09546634.2018.1506082
15. Dudley A.C., Griffioen A.W. Pathological angiogenesis: Mechanisms and therapeutic strategies // Angiogenesis. 2023. Vol. 26, N 3. P. 313–347. doi: 10.1007/s10456-023-09876-7
16. Han Q., Niu X., Hou R., et al. Dermal mesenchymal stem cells promoted adhesion and migration of endothelial cells by integrin in psoriasis // Cell Biol Int. 2021. Vol. 45, N 2. P. 358–367. doi: 10.1002/cbin.11492
17. Li J., Hou H., Zhou L., et al. Increased angiogenesis and migration of dermal microvascular endothelial cells from patients with psoriasis // Exp Dermatol. 2021. Vol. 30, N 7. P. 973–981. doi: 10.1111/exd.14329
18. Hern S., Stanton A.W., Mellor R.H., et al. In vivo quantification of the structural abnormalities in psoriatic microvessels before and after pulsed dye laser treatment // Br J Dermatol. 2005. Vol. 152, N 3. P. 505–511. doi: 10.1111/j.1365-2133.2005.06435.x
19. Gong J., Yang H., Qi D., et al. The association of serum vascular endothelial growth factor levels and psoriasis vulgaris: A protocol for systematic review and meta-analysis // Medicine (Baltimore). 2020. Vol. 99, N 33. P. e21565. doi: 10.1097/MD.0000000000021565
20. Mohta A., Mohta A., Ghiya B.C. Assessing the association between psoriasis and cardiovascular ischemia: An investigation of vascular endothelial growth factor, cutaneous angiogenesis, and arterial stiffness // Indian Dermatol Online J. 2023. Vol. 14, N 5. P. 653–657. doi: 10.4103/idoj.idoj_246_23
21. Zhu W.J., Li P., Wang L., et al. Hypoxia-inducible factor-1: A potential pharmacological target to manage psoriasis // Int Immunopharmacol. 2020. Vol. 86. P. 106689. doi: 10.1016/j.intimp.2020.106689
22. Griffioen A.W., Bischoff J. Oxygen sensing decoded: A Nobel concept in biology // Angiogenesis. 2019. Vol. 22, N 4. P. 471–472. doi: 10.1007/s10456-019-09692-y
23. Xian D., Song J., Yang L., et al. Emerging roles of redox-mediated angiogenesis and oxidative stress in dermatoses // Oxid Med Cell Longev. 2019. Vol. 2019. P. 2304018. doi: 10.1155/2019/2304018
24. Luengas-Martinez A., Ismail D., Paus R., et al. Inhibition of vascular endothelial growth factor-A downregulates angiogenesis in psoriasis: A pilot study // Skin Health Dis. 2023. Vol. 3, N 5. P. e245. doi: 10.1002/ski2.245
25. Kuang Y.H., Lu Y., Liu Y.K., et al. Topical sunitinib ointment alleviates psoriasis-like inflammation by inhibiting the proliferation and apoptosis of keratinocytes // Eur J Pharmacol. 2018. Vol. 824. P. 57–63. doi: 10.1016/j.ejphar.2018.01.048
26. Guillot X., Tordi N., Mourot L., et al. Cryotherapy in inflammatory rheumatic diseases: A systematic review // Expert Rev Clin Immunol. 2014. Vol. 10, N 2. P. 281–294. doi: 10.1586/1744666X.2014.870036
27. Kurz B., Berneburg M., Bäumler W., Karrer S. Phototherapy: Theory and practice // J Dtsch Dermatol Ges. 2023. Vol. 21, N 8. P. 882–897. doi: 10.1111/ddg.15126
28. Chua R.A., Arbiser J.L. The role of angiogenesis in the pathogenesis of psoriasis // Autoimmunity. 2009. Vol. 42, N 7. P. 574–579. doi: 10.1080/08916930903002461
29. Олисова О.Ю., Каюмова Л.Н., Смирнов К.В., и др. Общая криотерапия с использованием криокапсулы icequeen при различных дерматозах // Российский журнал кожных и венерических болезней. 2017. Т. 20, № 1. С. 15–20. EDN: YGTAIR doi: 10.18821/1560-9588-2017-20-1-15-20
30. Allan R., Malone J., Alexander J., et al. Cold for centuries: A brief history of cryotherapies to improve health, injury and post-exercise recovery // Eur J Appl Physiol. 2022. Vol. 122, N 5. P. 1153–1162. doi: 10.1007/s00421-022-04915-5
31. Hohenauer E., Costello J.T., Deliens T., et al. Partial-body cryotherapy (-135°C) and cold-water immersion (10°C) after muscle damage in females // Scand J Med Sci Sports. 2020. Vol. 30, N 3. P. 485–495. doi: 10.1111/sms.13593
32. Kujawski S., Newton J.L., Morten K.J., Zalewski P. Whole-body cryostimulation application with age: A review // J Therm Biol. 2021. Vol. 96:102861. doi: 10.1016/j.jtherbio.2021.102861
33. Zembron-Lacny A., Morawin B., Wawrzyniak-Gramacka E., et al. Multiple cryotherapy attenuates oxi-inflammatory response following skeletal muscle injury // Int J Environ Res Public Health. 2020. Vol. 17, N 21. P. 7855. doi: 10.3390/ijerph17217855
34. Tabisz H., Modlinska A., Kujawski S., et al. Whole-body cryotherapy as a treatment for chronic medical conditions? // Br Med Bull. 2023. Vol. 146, N 1. P. 43–72. doi: 10.1093/bmb/ldad007
35. Ho S.S., Illgen R.L., Meyer R.W., et al. Comparison of various icing times in decreasing bone metabolism and blood flow in the knee // Am J Sports Med. 1995. Vol. 23, N 1. P. 74–76. doi: 10.1177/036354659502300112
36. Knobloch K., Grasemann R., Spies M., Vogt P.M. Midportion achilles tendon microcirculation after intermittent combined cryotherapy and compression compared with cryotherapy alone: A randomized trial // Am J Sports Med. 2008. Vol. 36, N 11. P. 2128–2138. doi: 10.1177/0363546508319313

AUTHORS' INFO

*** Anna A. Brezhneva;**
address: 4/1 Bolshaya Pirogovskaya street, 119435 Moscow, Russia;
ORCID: 0009-0002-2489-1269;
e-mail: anna-brezhneva@mail.ru

Nikolay G. Kochergin, MD, Dr. Sci. (Med.), Professor;
ORCID: 0000-0001-7136-4053;
eLibrary SPIN: 1403-3031;
e-mail: nkocha@yandex.ru

Olga S. Yazkova, MD, Cand. Sci. (Med.);
ORCID: 0000-0002-9644-4778;
eLibrary SPIN: 9548-9076;
e-mail: olesha230808@mail.ru

Alexander A. Fadeev, MD, Cand. Sci. (Med.);
ORCID: 0009-0000-6619-5056;
e-mail: fadeevalek@yandex.ru

* Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

*** Брежнева Анна Александровна;**
адрес: Россия, 119435, Москва, ул. Большая Пироговская, д 4/1;
ORCID: 0009-0002-2489-1269;
e-mail: anna-brezhneva@mail.ru

Кочергин Николай Георгиевич, д-р мед. наук, профессор;
ORCID: 0000-0001-7136-4053;
eLibrary SPIN: 1403-3031;
e-mail: nkocha@yandex.ru

Яцкова Ольга Сергеевна, канд. мед. наук;
ORCID: 0000-0002-9644-4778;
eLibrary SPIN: 9548-9076;
e-mail: olesha230808@mail.ru

Фадеев Александр Александрович, канд. мед. наук;
ORCID: 0009-0000-6619-5056;
e-mail: fadeevalek@yandex.ru