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TREATMENT BASIS AND PATHOGENETIC BASIS OF AXIAL SPONDLITIS

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Abstract:
Spondyloarthritis (SpA) is a group of chronic inflammatory diseases of the spine, joints and entheses, characterized by common clinical, radiological and genetic features. The aim of this work was to analyze modern ideas about the etiology and pathogenesis of axial spondyloarthritis (axSpA) and pathogenetically based methods for improving their treatment. The presented information is necessarily based on information from many scientific journals. The information mainly included full-text articles in Uzbek, Russian and English. The following words were mainly used for the search. Axial spondyloarthritis, ankylosing spondylitis, axial spondyloarthritis, peripheral spondyloarthritis, genetic drug periparts, medical biological treatment, biological agents, AS pathogenesis, AS treatment, AS drug treatment, non-drug treatment methods and their Russian, Uzbek and English equivalents. The authors presented an analysis of the current treatment options for AS, the advantages and disadvantages of the current treatments, and their views on how to optimize them. Promising approaches for pathogenetic treatment of AS, including the elimination of autoreactive TRBV9+ T lymphocytes, their potential role in the treatment of the disease, their expected advantages and disadvantages, and possible future treatment options were discussed. The final section of the article was to present the authors' views on potential pathogenetic treatment options for AS.

Keywords: Spondyloarthritis, axial spondyloarthritis, peripheral spondyloarthritis, ankylosing spondylitis, TRBV9+ T-lymphocytes, macrophages, tumor necrosis factor α, interleukin 17.

Spondyloarthritis (SpA) is a group of chronic inflammatory diseases of the spine, joints, entheses, characterized by common clinical, radiological and genetic features [1]. Axial spondyloarthritis (axSpA) is a subtype of SpA with mandatory involvement of the axial skeleton structures in the inflammatory process [1]. Currently, based on the characteristics of the sacroiliac joints, two forms of axSpA are distinguished - non-radiological (nr-axSpA) and radiological (ankylosing spondylitis, AS). Based on the clinical features of the disease, special forms of axSpA are distinguished: psoriatic axSpA; axSpA associated with Crohn's disease or ulcerative colitis (inflammatory bowel disease (IBD)); reactive axSpA [1].

All axSpA are united by common pathogenesis pathways and, according to modern concepts, are related to diseases associated with the characteristics of the human major histocompatibility complex type I (Main Histological Complex-I, MHC-I), or MHC-I-associated diseases. In the treatment of MHC-I-associated diseases, a number of common approaches are used, related to the common pathogenesis of the diseases [2].

Current methods of drug treatment of axSpA include the use of non-steroidal anti-inflammatory drugs (NSAIDs), sulfasalazine (for peripheral involvement) and genetically engineered biological therapy (GEBT): tumor necrosis factor α (TNF-α) blockers and interleukin (IL) 17 blockers, as well as Janus kinase inhibitors [3, 4]. Despite the large number of drugs used to treat axSpA, the effectiveness rates are below target values - the number of people achieving low disease activity or remission in axSpA often does not exceed 20% even with GEBT, and about 18% of patients with axSpA are classified as "difficult to treat patients" [5, 6]. In this regard, there is a need to optimize approaches to the treatment of axSpA both by improving the understanding of the place and features of the use of drugs already recommended for use, and by developing new drug and non-drug methods for the treatment of axSpA. At the same time, treatment based on understanding the etiology and correction of the main pathogenesis pathways of axSpA seems to be the most promising. The aim of this work was to analyze modern concepts about the etiology and pathogenesis of axSpA and pathogenetically substantiated ways to improve their treatment.

Non-drug methods of treating axSpA Lifestyle correction. Quitting smoking, drinking alcohol, physical inactivity and normalizing body weight are promising, pathogenetically substantiated methods of treating axSpA related to lifestyle correction [3, 4, 7].Smoking is an independent universal factor that maintains systemic inflammation at all its stages (exudative inflammation, proliferative inflammation). Hypodynamia contributes to an increase in body weight with the development of its excess, which also triggers and maintains inflammation due to the hyperproduction of adipocytokines

and the formation of oxidative stress with increased lipid peroxidation. It has been shown that hypodynamia is an independent factor in the formation of the loss of the effect of GIBT [9]. Normalization of body weight helps reduce the severity of systemic inflammation by normalizing the level of adipocytokines. Achieving normal body weight is facilitated by a diet adequate in caloric content and composition, exercise and, in the presence of special indications (insulin resistance, diabetes mellitus, chronic heart failure), the use of glucagon-like peptide type I agonists (semaglutide, liraglutide, etc.) and other drugs that affect incretins (complex drugs currently under development).In addition to the direct positive effect on the activity and structural progression of axSpA, smoking cessation, normalization of physical activity and body weight in axSpA are measures to prevent cardiovascular morbidity and mortality among this category of individuals [7].The advantages of non-drug methods of treating axSpA are their general availability, high economic feasibility, and the absence of the risk of drug-induced damage to internal organs [12]. However, the practical implementation of non-drug treatment has a number of limitations that significantly reduce its value. The disadvantage of therapeutic exercise as a method of treating axSpA is low patient compliance with this treatment method, the impossibility of creating general recommendations for all patients, and a high risk of increased activity and complications if the exercises are performed incorrectly [3, 4, 13, 14]. Patients of different ages, with different disease activity, with different structural changes in the axial skeleton and different concomitant conditions (osteoporosis, degenerative disc disease, hip dysplasia, etc.) need different types of therapeutic exercises [13, 14]. In this regard, each patient with axSpA requires individual selection of exercises by a doctor, which, in the absence of treatment standards, leads to a sharp increase in the role of the human factor in therapeutic exercise. It is currently not possible to level this factor, so it was decided that any therapeutic exercise is better than no exercise, and that training with a trainer and in a group is more effective than training at home without professional supervision [4]. In addition to low adherence to treatment and the lack of the possibility of standardizing therapeutic exercise, there is another risk - a rapid increase in the load, an inadequately selected load, a violation of technique or irregular exercise performance can lead to the opposite effect of therapeutic exercise - an increase in spasm of overloaded muscles and an overload of the spinal column with an increase in posture disorders, which will lead to increased tension of the involved ligaments, tendons, capsules and will aggravate the effect of "Koebnerization", increasing the biomechanical component of axSpA activity. In these situations, an increase in axSpA activity is observed, and the progression of structural changes in the axial skeleton is accelerated [13, 14]. Another factor limiting the benefits of therapeutic exercise is the inability of patients with late stages of the disease to follow most of the recommendations - for example, patients with hyperkyphosis and ankylosis of the spine are limited in performing most exercises due to the high risk of syndesmophyte fractures and other complications.Manual therapy. Osteopathy. Similar limitations (lack of sufficient evidence base, low standardization with an increasing role of the human factor, impossibility of regular use, risk of secondary trauma and overload of the musculoskeletal system) exist in other non-drug treatment methods: manual therapy, osteopathy. Isolated studies on

the benefits of acupuncture for axSpA do not allow the method to be included in the treatment of axSpA, although the effect of the needle on the muscles in theory can lead to muscle relaxation and a decrease in the overload of the axial skeleton.Physiotherapy. A low level of evidence limits the use of physiotherapy for the treatment of axSpA [4]. Taking into account the information on anti-inflammatory activity, we believe that the use of laser therapy, hydrocortisone electrophoresis or hydrocortisone ultraphonophoresis to reduce local inflammation in individual entheses or joints is promising. However, the evidence base for these methods in axSpA is scant; they need to be studied in studies involving a large patient population. The use of shock wave therapy for the treatment of enthesitis in axSpA also requires accumulation of sufficient evidence - at present, the small amount of evidence does not allow us to recommend this method for the treatment of axSpA - theoretically, it can both have a positive effect due to its anti-inflammatory potential and stimulate MHC-I-associated inflammation due to microdamage to the enthesis tissue during the procedure, contributing to the progression of the disease [4]. Local radiation therapy, laser therapy and shock wave therapy are still considered promising methods for the treatment of resistant enthesitis (especially in the heel area). The methods mentioned above are not included in the recommendations for the treatment of axSpA, but are described in some studies as effective in the long term due to the ability of X-rays and long-wave laser beams to penetrate both vascular and avascular parts of entheses, providing not only anti-inflammatory but also antiproliferative effects on the specified area. Clinically, according to research data, the local effect of X-rays or lasers is manifested by a decrease in local inflammation, slowing the growth of exostoses ("heel spurs") and a decrease in pathological mineralization of the plantar aponeurosis. It should be noted that, given its greater safety, preference is given to laser therapy, while local radiation therapy is used in exceptional cases [15].

Systemic radiation therapy as a method for achieving remission in axSpA is prohibited for use, despite its high efficiency, due to a significant increase in the risk of complications (primarily the risk of developing malignant lymphomas) [16].Drug treatments for axSpA Methods of drug treatment for axSpA according to Russian and international recommendations.

At the next stage of the disease, the impact of a trigger factor capable of enhancing the T-lymphocyte imbalance in a person predisposed to axSpA or activating additional (monocyte-macrophage) links of immunity can shift the balance between anti-inflammatory and pro-inflammatory links towards pro-inflammatory reactions. Of particular importance in this case is the activation of pro-inflammatory expression of the HLA-B27 gene due to blockade of the Clip receptor by antibodies to CD74, as well as increased expression of the IL-17 and IL-23 genes and accelerated peptide synthesis with increased antigen presentation by dendritic cells and macrophages due to activation of the ERAP1 and ERAP2

genes (Fig. 1) [10, 11, 18, 19]. The recognized factors of activation of the indicated pathological processes are chronic overload, microtraumatization or severe trauma, which lead to an increase in the local activity of tissue macrophages involved in the local increase in the concentration of TNF-α; infections, the resolution of which stimulates Th17 lymphocytes and increases the concentration of IL-17 above the threshold (chlamydia, dysentery, salmonellosis) and chronic neuropsychic overstrain (see Fig. 1).Despite the lack of a clear understanding of the classification of NSAIDs as symptomatic or basic agents for the treatment of axSpA, modern recommendations classify NSAIDs as first-line drugs in the treatment of axSpA. Taking NSAIDs for axSpA is mandatory until the clinical and laboratory manifestations of SpA are resolved; the need to continue treatment after the normalization of the clinical laboratory picture is determined by the doctor in accordance with the specific clinical situation. The only factor limiting the prescription of NSAIDs in patients with axSpA may be the presence of contraindications to drugs in a particular patient. It should be noted that it is this provision that regulates the impossibility of using NSAIDs in axSpA associated with IBD (Crohn's disease or ulcerative colitis) [23]. Other anti-inflammatory drugs — glucocorticosteroids (GCS) — are used in axSpA only in the form of intra-articular or periarticular injections in the presence of a small number (3 or less) of zones of local inflammatory activity resistant to systemic and local forms of NSAIDs. Local use of GCS is justified in the presence of contraindications to NSAIDs. Systemic use of GCS in axSpA in low doses is ineffective, and the use of high doses is limited by an unreasonably high risk of complications and is possible only in special situations (uveitis, IBD when immediate initiation of GIBT is impossible) [3, 4, 22].

Sulfasalazine is a drug used only for axSpA with peripheral involvement. Pathogenetically, its use is determined by the drug's ability to influence the normalization of intestinal microbiota, the role of which in the development of axSpA is actively discussed. At the same time, the use of sulfasalazine is limited by its inability to influence inflammation of the axial skeleton, as well as relatively low clinical efficacy [3, 4]. Genetically engineered biological and targeted drugs are among the drugs whose use requires a physician to have a deep understanding of the clinical and pathogenetic relationships in axSpA. Returning to the clinical and pathogenetic relationships, it should be noted that for the correct selection of GIBT, it is important for the clinician to determine what type of inflammation the patient is facing. Patients with high-grade inflammation are characterized by a vivid clinical picture with high-intensity pain syndrome in the back and joints, pronounced local exudative inflammation with joint involvement (synovitis, joint swelling), prolonged and pronounced morning stiffness, signs of asthenia, weight loss up to muscle atrophy. A patient with such inflammation may have an elevated body temperature (see Fig. 1). The most important laboratory marker of high-grade inflammation is an increase in the CRP level by 2 times or more (relative to the upper limit of the reference interval), anemia of chronic inflammation may be recorded, and in the case of a long-term course of the disease - systemic osteoporosis. The pathogenetic basis of high-grade inflammation is a powerful activation of the monocyte-macrophage link of immunity with a marked increase in the concentration of TNF-α both in tissues and in the blood serum, with simultaneous activation of the T-lymphocyte link with an increase in the level of IL-17 and IL-21/22 in the blood serum (see Fig. 1) [24, 25]. It is the high level of TNF-α that determines the severity of the general systemic and acute phase reaction in patients with axSpA [24, 25].

Taking into account the pathogenetic point of view, TNF-α blockade (infliximab, adalimumab, golimumab, certolizumab pegol and etanercept) seems to be the most justified in high-grade inflammation [4]. Its advantage is the ability to quickly reduce the signs of systemic inflammation, which leads to a rapid normalization of the patient's well-being: pain syndrome, stiffness, general weakness and other symptoms subside, the CRP level is normalized, the hemoglobin level is restored. Monoclonal antibodies to TNF-α (adalimumab, golimumab, infliximab, certolizumab pegol) cope well with inflammation in extraskeletal manifestations of axSpA (psoriasis, IBD, uveitis) [3, 4, 23, 26]. At the same time, TNF-α blockade in axSpA has a number of limitations, among which it is worth noting a decrease in anti-tuberculosis immunity associated with the fact that the limitation of the tuberculosis process during infection with Mycobacterium tuberculosis occurs primarily through the formation of a granuloma, the formation of which is triggered by tissue (alveolar) macrophages upon contact with the infectious agent by increasing the production of soluble and membrane fractions of TNF-α [4, 26]. Thus, a decrease in the concentration of TNF-α reduces the likelihood of granuloma formation and increases the risks of mycobacterium dissemination [26]. Another pathogenetically determined limitation of TNF-α blockade is its inability to quickly reduce the activity of the T-lymphocyte system, due to which, against the background of a decrease in the concentration of TNF-α and the general inflammatory reaction in axSpA, the level of IL-17 and IL-22 remains elevated for a long time [27, 28]. It is important that the concentration of IL-23 and PgE2 decreases against the background of TNF-α blockade [28]. There are several clinical consequences of non-unidirectional dynamics of proinflammatory cytokines:

Sequential use of GIBT with different mechanisms of action. Taking into account the features of the immunopathogenesis of axSpA, the possibility of sequential use of GIBP with different mechanisms of action to achieve the maximum treatment effect is constantly discussed. Indeed, sequential use of TNF-α blockers in the presence of high-grade inflammation with subsequent transition to IL-17 blockade after a decrease in the severity of systemic inflammation may be promising. Sequential use of TNF-α blockers and monoclonal antibodies to the TRBV9 segment of the T-lymphocyte receptor cannot be ruled out. At the same time, the implementation of promising pathogenetic strategies requires a thorough study of the benefit/risk ratio for the patient with the implementation of clinical trials in accordance with Russian and international standards. Normalization of intestinal microbiota. The use of autoprobiotics as a method of maintaining remission in axSpA by normalizing epigenetic mechanisms of proinflammatory pathogenesis pathways may theoretically be promising. At present, despite the powerful theoretical justification for the

appropriateness of such treatment, the creation of drugs capable of inducing or maintaining remission by normalizing intestinal microbiota has failed. Attempts to transplant microbiota in axSpA have also been unsuccessful .In this regard, the most promising method of basic treatment of axSpA currently being developed is the blockade of key T-cell links in the immunopathogenesis of spondyloarthritis. The technology of blockade of autoreactive TRBV9+ T-lymphocytes developed by Russian scientists can potentially be effective in patients with the presence of the HLA-B27 antigen [43–45]. This T-cell blockade can potentially be an effective disease-modifying effect, ideologically aimed not so much at induction as at preventing pathological cytokine activation due to targeted point depletion of the main autoimmune clones of T-lymphocytes. Non-interference of treatment with the physiological parts of the immune response determines the possibility of healthy functioning of the immune system of a patient with axSpA during treatment. The use of such basic technologies looks especially promising for the induction and maintenance of remission in patients with recently developed early SpA, including low-grade inflammation. It is possible that the elimination of TRBV9+ T lymphocytes in patients with high-grade inflammation may require separate induction of remission with TNF-α or IL-17 blockers. This is especially interesting in light of the fact that previous attempts to develop molecules targeting the blockade of several cytokines at once have not yet been successful.

It should be noted that at present, the possibilities of combined blockade of several cytokines (currently, this option is limited by the risk of side effects) and the possibilities of sequential planned change of cytokine blockers with different mechanisms of action have not been exhausted in "difficult-to-treat patients" with axSpA. Future clinical trials are needed to develop optimal regimens of combined GIBT or targeted therapy for axSpA.

Thus, at present, it should be noted not only the presence of difficulties in the treatment of axSpA, but also the presence of encouraging promising directions for their correction. Rapid development of fundamental science and genetic engineering technologies increases the requirements for the doctor regarding a deep understanding of clinical and pathogenetic relationships in axSpA. The accuracy of the choice of treatment and its subsequent effectiveness and safety depend on the correct understanding by the doctor of the clinical course of the disease in each individual patient.

CONCLUSION

At present, the concept of treating axSpA "until the target is reached" cannot be considered fully realized, which determines the need to develop new methods of treating axSpA Studying the etiology and pathogenesis of axSpA is the most promising way to create new approaches to treatment. The treatment approaches currently being developed allow us to hope for a significant improvement in the prospects of patients with axSpA in the near future.

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