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## ABSTRACT

The presented literature review examines the latest data on the pathogenesis, diagnosis and treatment of ankylosing spondylitis (AS), data on the comparative efficacy of modern drugs, and physiotherapy methods used in the treatment of AS. A search was carried out using the OVID platform in MEDLINE, including the Scopur database, Springer Nature, PubMED and the Cochrane Library Central Database (Wiley version), Elibrary with the analysis of data on the efficacy and safety of therapy for patients with AS.

**Key words:** ankylosing spondylitis, pathogenesis, diagnosis, treatment.

## INTRODUCTION

Ankylosing spondylitis (AS) (Bekhterev's disease) is a systemic chronic inflammatory disease of the axial skeleton with frequent involvement in the pathological process of entheses and peripheral joints, as well as other organs and systems [6, 7, 20]. This is a common chronic rheumatic disease of adults with a progressive course that leads to significant disability. Therefore, the prognosis largely depends on the early diagnosis and the immediate appointment of adequate therapy. The prevalence of SpA in the world varies widely and ranges from 0.06 to 6% [4, 16, 32, 33]. The ratio of sick men and women is on average 9:1, in representatives of the white race, the disease with obvious clinical forms is observed from 0.15 to 1.5% of the population, in Poland from 0.05 to 0.23%, in

Finland - is 0.15%, in Norway — 1,4%) [19, 21, 24, 25]. The disease develops mainly at the age of 20-40 years, extremely rarely after 45 years [2, 12, 25]. At the same time, in one study from France, the overall frequency of spondylitis was 2.4 per 100 thousand of the population and increased with increasing age, reaching 6.5 per 100 thousand among patients aged 50-70 years [21, 27, 29]. As described above, two factors (genetic and environmental) are mainly involved in the pathogenesis of AS. Two main environmental factors: mechanical stress and bacterial infections trigger the pathogenesis of AS. Spondylitis in adults is most often the result of hematogenic introduction of microorganisms from the distal focus into the adjacent space of the vertebral disc, since the disc itself is avascular [12, 25, 29]. AS belongs to the group of mixed auto-inflammatory-autoimmune rheumatic diseases associated with HLA class I antigens, the pathogenesis of which is based on a combined defect of activation of the innate and acquired immune response [1, 8]. There are two theories of pathogenesis explaining the important role of HLA B27 in the development of the disease. According to the receptor theory, the HLA B27 antigen is a receptor for an etiological damaging factor [14, 25]. The resulting complex leads to the production of cytotoxic T-lymphocytes, which can then damage cells or tissue sites where the B27 antigen molecules are located. According to the molecular theory of mimicry, bacterial antigen or some other damaging agent in combination with the HLA molecule may have properties similar to HLA B27 and be recognized by cytotoxic T-lymphocytes as HLA B27, or reduce the immune response to the disease-causing peptide [14, 25]. As a result, an immuno-inflammatory process develops. Most often, it begins with damage to the sacroiliac joints, and then intervertebral, rib-vertebral, and rarely peripheral joints are involved. Initially, infiltration by lymphocytes and macrophages occurs, and then an active fibroplastic process develops with the formation of fibrous scar tissue, which undergoes calcification and ossification. The main pathomorphological manifestations of the disease are inflammatory enthesopathies, inflammation of the bones forming the joint, as well as synovitis. Subsequently, fibrous and bony ankylosis of the joints of the axial

skeleton develops, less often - peripheral joints, ossification of the ligamentous apparatus of the spine occurs early [12, 14, 25]. The key pathogenetic markers of AS are: genetic polymorphisms (HLA-B27, aminopeptidase ERAP1 gene and genes responsible for activation of the pathological cytokine axis of interleukins), markers of inflammation (C-reactive protein, serum amyloid protein, calprotectin, soluble form of cytotoxic T-lymphocytic antigen), proinflammatory cytokines (tumor necrosis factor (α– TNFa), interleukins (IL) IL17, IL23, IL21, IL22, IL6), markers of bone, cartilage and synovial tissue metabolism, autoantibodies (antibodies to CD74, microbial antigens, citrullinated proteins) [1, 13]. In recent years, much attention has been drawn to Th17 cells synthesizing IL17 [1, 16]. According to the authors, pathological activation and expansion of Th17 cells play a leading role in the development of a wide range of human immune-inflammatory diseases (IID). Indeed, 55% of AS patients showed a decrease in bone mineral density: in 19% - corresponding to the criteria of osteoporosis, in 36% - osteopenia [22]. At the same time, degradation occurs in the bone tissue, manifested by changes in the content of osteocalcin and C-terminal telopeptides of type I collagen, as well as the main regulators of osteoclastogenesis (osteoprotegerin/ligand receptor activator of nuclear factor kappa-b) in patients with AS [23]. The progression of AS is associated with the proliferation of bone tissue, the growth of syndesmophytes (and/or enthesophytes) and ankylosing of the joints of the spine. Patients with AS also have extra-skeletal symptoms: in 10-30% – eye damage, disorders of the cardiovascular system - in 20-22% of cases; pneumofibrosis - 3-4%; kidneys - in 5-31% of patients and osteoporosis [5, 28]. According to the literature data, in recent years, in countries such as Germany, France, Spain and the Netherlands, an active study of cohorts of patients with early ankSpA has been conducted, which compares the clinical manifestations of nr-ankSpA with SPA [34]. The authors found no differences in clinical manifestations and activity of the disease according to the BASDAI index between the above groups. At the same time, nr-axSpA has a more balanced distribution by gender than SpA, which is mainly characteristic of males [30]. In the German cohort

GESPIC (2009), in contrast to the French and Dutch studies, patients with SpA showed higher laboratory activity, determined by the level of CRP, and a lower functional status [8, 11]. To find out whether nr-axSpA is an early manifestation of SpA, 132 patients were analyzed [14]. After 12 months, 69 patients remained. Of these, 63 patients were positive for HLA-B27, 41 patients were diagnosed with SpA, 28 with nr-axSpA. According to the main clinical parameters (the presence of arthritis and enteritis), disease activity (according to the BASDAI index, ASDAS CRP) and functional status (BASFI index), the patients of the two groups did not differ. After 12 months of follow-up, all indicators of inflammatory activity decreased by almost 2 times in both groups. 7 (25%) patients with nr-axSpA developed radiologically detectable sacroiliitis in 12 months and the diagnosis of AS was confirmed. Initially, among them, 2 (28.5%) people had signs of active SI detected by magnetic resonance imaging (MRI), 4 (57.1%) had chronic SI, and 1 (14.4%) had no pathological changes according to MRI data. Based on the data obtained, the authors conclude that nr-axSpA may be an early stage of AS [14]. At the beginning of the disease, in the presence of inflammatory back pain, inflammation in the bone structures of the spine and/or sacroiliac joints can only be visualized using MRI (pre radiological stage of AS) [17]. At the next stage, bone structural changes appear and SI can be detected by X-ray examination. The last stage is the appearance of syndesmophytes. These three stages can be designated as initial (preradiological stage), expanded (the appearance of rSI) and late (syndesmophytic formation). Accordingly, in patients with a change in the stage of the disease, the prognosis and therapeutic tactics change. Data from a number of studies in Russia have shown that the diagnosis of AS is made with a significant delay. So, in the city of Khabarovsk, it is exhibited on average 9.7 years after the onset of the disease. This may indicate a lack of awareness of primary care physicians about this disease. Thus, according to the Moscow study, the diagnosis was established on average after 8.1± 6.0 years, and in Kazan, where a system of continuous educational programs among primary care doctors was introduced, much earlier - after 4.2± 1.2 years [9, 15]. The same statement is shown in the

work of Belarusian scientists. According to the literature, among rheumatological patients who first sought medical help, rheumatic diseases were incorrectly diagnosed at the outpatient stage in 41% of cases. Only 49% of patients had a coincidence of diagnoses after examination by a specialist. A late referral to a rheumatologist also leads to an increase in chronic forms of the disease [2, 9, 11, 16]. Spondylitis is usually diagnosed against the background of persistent back pain resistant to conservative treatments and elevated markers of inflammation, accompanied or not accompanied by fever. Overview radiography of the spine does not have sufficient sensitivity for early diagnosis of spondylitis. MRI of the spine is often required to confirm the diagnosis [7, 17, 18]. The international expert group ASAS Assessment of Spondylo Arthritis International Society), established more than 15 years ago, has had a significant impact on solving various problems associated with ankylosing spondylitis, on its initiative, new approaches to the treatment of the disease and new diagnostic and therapeutic principles are being actively developed [31].For the diagnosis of ankylosing spondylitis (AS), modified New York criteria are used at the present stage, where the main condition is the presence of SI - unilateral stage III-IV or bilateral stage II according to Kellgren [26]. BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) is used to determine AC activity. BASDAI values exceeding 40 points indicate a high activity of the disease. In 2009, the European Anti-Rheumatic League proposed the ASDAS index (Ankylosing Spondilitis Disease Activity Score), which takes into account not only clinical manifestations of AS, but also such laboratory indicators of disease activity as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). If the ASDAS indicators are < 1.3 points, the activity of AS is low, from 1.3 to 2.1 points - moderate, from 2.1 to 3.5 points - high, > 3.5 points - very high, a high level of ESR, CRP and circulating immune complexes is considered a sign of inflammatory damage to the joints and spine in AS. Rheumatoid factor is usually not detected [2].

Modern diagnostic approaches make it possible to diagnose axial spondyloarthritis (aksSpA) at the X-ray stage corresponding to ankylosing

spondylitis in (AS), while early diagnosis of non-pathogenic aksSpA (nr-aksSpA) is still difficult. This leads to the need to search for new laboratory biomarkers for early diagnosis of spondyloarthritis, which include the recently described autoantibodies to the CD74 antigen. Scientists from Saratov Kuznetsova D.A., Lapin S.V., Gaidukova I.Z. [10] showed the clinical and diagnostic significance of autoantibodies to CD74 in axial spondyloarthritis. IgA-CD74 autoantibodies were analyzed in serum samples of 140 patients with aksSpA: 68 with AS, 46 with nr-aksSpA, 26 with psoriatic arthritis (PsA) and 37 healthy representatives of the control group, in whom the signs of aksSpA were clinically completely excluded. The average concentrations of IgA autoantibodies to CD74 in patients with aksSpA and nr-aksSpA were 3.5±3.0 and 3.8±2.9 units/ml, respectively, which significantly differed significantly from patients with PsA and healthy individuals - 2.1±1.4 and 1.3±1.4 units/ml, respectively ($p<0.05$). According to the authors, with a threshold value of IgA autoantibodies to CD74 of more than 2.0 U/ml with aksSpA, diagnostic sensitivity was 64.4%, specificity was 89.2%, and the risk factor for a positive result was 5.9, whereas in patients with nr-aksSpA at a concentration of 1.7 U/ml - 73.1%, 84% and 4.5, respectively. IgA autoantibodies to CD74 antigen are associated with axSpA, but not with PsA, which makes it possible to use this marker for the diagnosis of axial spondyloarthritis, as well as for differential diagnosis between axial spondyloarthritis and ankylosing spondylitis. According to scientists Alexandrova E.N., Novikov A.A. (2017) [1] currently, key pathogenetic biomarkers of AS (therapeutic "targets") have been identified, which include TNFa, IL17 and IL23. Among diagnostic and prognostic laboratory biomarkers of AS, HLA-B27 (for early diagnosis of the disease) and C-reactive protein (CRP; for assessing activity, risk of radiological progression and effectiveness of therapy) are of the greatest importance in clinical practice [3]. CD74 antibodies are a new biomarker that allows for the diagnosis of axial SpA at an early stage with high sensitivity and specificity. A number of laboratory biomarkers, including calprotectin, matrix metalloproteinase 3 (MMP3), vascular-endothelial growth factor, Dickkopf-1 (Dkk-1) and type II collagen C-terminal

telopeptide (CTX II), do not sufficiently reflect the activity of the disease, but can be predictors of the progression of structural changes in the spine and sacroiliac joints in AS. Monitoring the level of calprotectin in the blood makes it possible to effectively predict the response to therapy with TNF inhibitors and monoclonal antibodies to IL17A. The prospects for laboratory diagnostics of AS are associated with the clinical validation of candidate biomarkers in the course of large prospective cohort studies and the search for new proteomic, transcriptomic and genomic markers based on innovative molecular and cellular technologies.

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