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The Role of Il-17 In Pathogenesis and Progression of Ankylosing Spondylitis

Saidrasulova G. B.
Tashkent medical academy

Annotation: Ankylosing spondylitis (AS) is a chronic inflammatory disease of the joints. It especially affects the sacroiliac joints and spine, as well as peripheral joints and visceral organs. AS progressively leads to inflammatory lesions and grows syndesmophytes, which cause disability and decrease quality of life. Besides, in advanced stages of disease may be accompanied with comorbidities, various disorders of heart conduction system and osteoporosis, malignancies and different complications as fracture of syndesmophytes, vision loss due to acute uveitis, aortic valve regurgitation. Early diagnosis and treatment may prevent or decrease functional disability of patients. For this need understand deeply the pathogenesis of disease. Below is given the role of IL-17 under pathways of AS.

Keywords: axial spondyloarthritis; inflammation; C-reactive protein; interleukin-17; HLA-B27.

Introduction.

The concept of seronegative spondyloarthritis (SpA) was introduced to medicine in 1974 by Moll and his colleagues, which includes subtypes belonging to the SpA group [2].

These subtypes include the well-known reactive arthritis, psoriatic arthritis, arthritis associated with inflammatory bowel diseases, ankylosing spondylitis (AS), and undifferentiated arthritis. These subtypes are unified by similar clinical signs and the presence of the HLA-B27 gene. In 1990, based on the clinical signs of SpA, Amor and the ESSG (European Spondyloarthritis Study Group) divided SpA into two main groups: axial SpA, which primarily affects the spine and sacroiliac joints (SIJ), and peripheral SpA, which predominantly affects peripheral joints [1,3]. However, due to the inconvenience of using this classification, the ASAS diagnostic criteria were introduced in 2009. According to these criteria, axial SpA is classified as non-radiographic or radiographic axial SpA, depending on the development of radiological signs. Axial SpA consists of two stages: the early stage, involving inflammation in the SIJ, and the advanced stage, characterized by structural changes. Thus, the radiographic stage of AS corresponds to the advanced stage of axial SpA [4].

The distinct feature of AS compared to other subtypes is the manifestation of symptoms specifically associated with spinal disease. These symptoms include quadratization of vertebral bodies, erosion, and syndesmophyte growth along the edges of vertebral bodies. In general, in AS, progressive and irreversible structural changes in the spine result in reduced physical mobility and decreased quality of life for patients.

AS primarily affects young men, occurring up to four times more frequently than in women. However, recent studies suggest this ratio has updated to 2:1, and in non-radiographic axial SpA, the gender ratio is reported to be equal [5]. AS has been found to occur more frequently among individuals aged 15-35 [13]. The disease's initial symptoms are significantly more prevalent among patients under 25, while its onset sharply decreases after the age of 45. In Europe, the delay from symptom onset to diagnosis averages 8-11 years [14], whereas in the United States, this delay is approximately 13 years [15]. The reasons for these diagnostic delays include the widespread prevalence of chronic inflammatory back pain, the subtlety of clinical signs, and the absence of specific markers for AS. Clinical symptoms of AS can also serve as primary distinguishing signs for other SpA subtypes, complicating early

diagnosis. Diagnostic delays inevitably postpone treatment measures, leading to not only physical but also psychological and economic challenges for patients and their families.

The global prevalence of AS is 0.1-1.4%. In Uzbekistan, AS cases were reported at rates of 6.3 per 100,000 in 2016, 10.2 in 2018, and 12.8 in 2020. The highest prevalence was recorded in Tashkent city, Tashkent region, Samarkand region, and Surkhandarya region. In Uzbekistan, AS ranks third after osteoarthritis and rheumatoid arthritis. Despite treatment efforts, 20-40% of patients, including those receiving gene-engineered biological therapy, show inadequate or ineffective responses. Ankylosis is a progressive process that gradually restricts mobility and occupational capability. According to various studies, 15 years or more after disease onset, 20.5% to 56% of patients become disabled, with the average age of disability being 46.3 years.

A reliable diagnosis of AS requires the detection of radiological signs of sacroiliitis. The stage preceding these radiological signs is referred to as the non-radiographic stage or the early stage of AS. Transition from non-radiographic axial SpA to AS is slow and time-dependent, with studies indicating that 5.1% of patients transition within 5 years and 19% within 10 years [6]. In general, inflammatory back pain is one of the earliest and most persistent symptoms of AS. However, this symptom is also characteristic of many other diseases, complicating diagnosis. Globally, axial SpA accounts for 5% of patients with inflammatory back pain [7]. The wide range of causes of inflammatory back pain contributes to frequent diagnostic delays or misdiagnoses. Additionally, AS often presents with other SpA symptoms, further complicating early diagnosis [13]. As a result, the time lost during delayed diagnosis leads to irreversible pathological new bone formation in the spine and SIJ, accompanied by decreased spinal mobility, persistent pain, fatigue, depression, and reduced quality of life [8].

Early diagnosis of AS and timely use of disease-modifying biological drugs can prevent irreversible changes, functional impairment, and late-stage complications in the spine [16]. AS diagnosis is based on clinical, laboratory, and instrumental examination methods. Various diagnostic criteria are used; however, the 1984 modified New York criteria are effective for diagnosing advanced AS but insufficiently sensitive for diagnosing the non-radiographic stage. The 2009 ASAS criteria are more sensitive and specific but are not widely used due to several reasons [9]. Factors like the presence of inflammatory back pain, a family history of the disease, responsiveness to anti-inflammatory drugs, and the detection of enthesitis complicate the differentiation of non-radiographic axial SpA from fibromyalgia or mechanical back pain [10]. Furthermore, MRI-detected inflammatory signs in the SIJ are nonspecific, as significant inflammatory signs (osteitis) can also be found postpartum, in athletes, in pathological degenerative arthritis, and after trauma [11-12]. Studies by Korotaeva and others indicate that delayed diagnosis, limited access to biological agents, and reduced quality of life due to disease activity are challenges faced by AS patients in Europe and America as well [17]. Diagnostic delays lead to increased functional impairment and deteriorated quality of life [18]. Early diagnosis and treatment initiation for AS can mitigate potential complications, improving patient outcomes [19].

The IL-17 cytokine family consists of six members (IL-17A-F) and interacts with five types of receptors in the body [20]. These cytokines not only play a protective role against various pathogens but are also essential for the modification of T-helper cells [21].

IL-17 is a pro-inflammatory cytokine that plays a crucial role in the body's defense mechanisms, particularly in protective surfaces, tissue repair, anti-cytokine immune reactions, and the pathogenesis of various inflammatory diseases [1]. One such disease is ankylosing spondylitis (AS). IL-17 is also involved in immune responses against fungal and bacterial infections [23].

Many genetic defects related to IL-17 have been identified, with some leading to distinct manifestations of impaired immune responses to fungal infections. For instance, chronic mucocutaneous candidiasis is associated with mutations in the IL-17A gene [24]. Individuals with this gene mutation experience recurrent or persistent inflammation in mucous membranes, nails, and skin [2]. Research involving IL-17 inhibitors has shown no significant increase in other specific pathogens apart from Candida [3].

IL-17A, a member of the IL-17 cytokine family, plays a pivotal role in the damage to skin, joints, and periarticular tissues in the pathogenesis of spondyloarthritis (SpA) [25]. In AS, simultaneous bone erosion and pathological ossification occur in various anatomical sites, with IL-17 participating in these processes. Experimental studies on arthritis have demonstrated that IL-17 induces bone resorption [4]. Recent findings suggest that IL-17A stimulates RANKL expression in osteoclast precursors and blocks the Wnt signaling pathway, thereby inhibiting osteoblast activation [5].

The primary source of IL-17 in SpA is adaptive immune cells, contributing to the chronicity of the disease. Increased Th17 cell expression has been identified in SpA [26]. Elevated levels of Th17 cells and IL-17A have been found in the skin and blood of psoriasis patients, as well as in the blood and synovial fluid of AS and psoriatic arthritis (PsA) patients [27]. This indicates a self-sustaining loop where Th17 cells and IL-17A production are amplified [28]. However, further research is needed to determine which Th17 subtypes play a dominant role in AS and PsA pathogenesis [29].

CD8+ T cells producing IL-17A have been detected in the synovial fluid of inflamed joints in AS and PsA patients, with their levels correlating with disease activity. However, this phenomenon is not observed in rheumatoid arthritis patients [30,31]. MAIT cells producing IL-17A have been identified in the blood and skin of psoriasis patients and the synovial fluid and blood of AS patients, where IL-17 production depends on IL-7 [33]. Studies suggest that immune cells capable of producing IL-17 are not scarce, as neutrophils do not produce IL-17A mRNA or protein even under strong stimulation [34].

Recent findings show that enthesitis develops due to local immune cell activation under significant mechanical stress [35]. In SpA, local immune cells continuously produce IL-17A in a closed-loop manner, resulting in chronic inflammation. In contrast, enthesitis caused by repetitive mechanical movements, such as "tennis elbow," resolves abruptly without the chronicity seen in SpA [36]. This underscores the role of genetic factors in the pathological process alongside immune responses. Specific triggers stimulate local immune cells to produce IL-17 and other inflammatory cytokines, such as IL-23 and PGE2 [36].

Preclinical mouse studies have shown that IL-23 expression in the liver stimulates local T cells in entheses to produce IL-17A and other inflammatory mediators, exacerbating SpA [37]. High IL-17A production by γ/δ T cells in damaged areas has been associated with increased bone regeneration [38,39]. Mouse models of inflammatory arthritis have demonstrated that the IL-23/17 axis leads to enthesitis [40], while other models show TNF-α production from myeloid and stromal cells in entheses without T-cell involvement [41,42].

The prolonged inflammation in entheses results in both erosion and new bone formation, with IL-17A playing a complex role in this process [43]. However, experimental studies on arthritis have shown that IL-17A primarily stimulates bone resorption [44,45]. IL-17A induces RANKL expression while inhibiting Wnt signaling, blocking osteoblast activation and promoting pathological bone formation [46,47,48].

Clinical trials involving PsA patients treated with IL-17A inhibitors for 24 months have demonstrated reduced or halted radiographic progression [49]. The exact role of IL-17A in new bone formation in AS and PsA remains unclear, with conflicting experimental results. Some researchers suggest that IL-17A enhances osteoblast differentiation in local stem cells, potentially activating the JAK2/STAT3 signaling pathway associated with osteogenesis [50,51].

Clinical and experimental studies reveal that blocking IL-17A reduces pathological new bone formation [50]. Anti-IL-17 and anti-IL-17A receptor antibodies are currently used to treat psoriasis, PsA, and AS, as IL-17 plays a crucial role in the development of these diseases. The IL-17 inhibitor secukinumab has shown efficacy in AS patients, with a low immunogenicity effect and no interference from previously used TNF-α inhibitors [52].

Pain is a primary clinical feature in AS and PsA. However, the intensity of pain does not correlate with inflammation or radiographic markers in these patients [53]. Moreover, neuropathic pain has also been

diagnosed in these patients, alongside inflammatory pain [54]. IL-17A modulates inflammatory pain by directly enhancing nociception and hyperalgesia through secondary mediators [55,56,57,58].

Preclinical studies on mice have observed IL-17RA and IL-17RC expression in neuronal cells in response to inflammation [59]. Clinical trials have demonstrated a significant reduction in pain in AS and PsA patients treated with IL-17A inhibitors [61,62]. However, it is unclear whether this pain reduction is due to decreased neuropathic expression or reduced inflammation.

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