

Research Progress in the Treatment of New Bone Formation of Ankylosing Spondylitis

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Abstract Ankylosing spondylitis (AS) has a very high disability rate. How to effectively inhibit the formation of new bones has become a difficult point in clinical treatment. In recent years, research has shown that different treatment plans can have an impact on inhibiting new bone formation. In this paper, the different effects of new bone formation in the treatment of AS with traditional Chinese and Western medicine are systematically listed.

Key words Ankylosing spondylitis, New bone formation, Treatment

1 Introduction

Ankylosing spondylitis (AS) is an autoinflammatory disease that involves multiple systems mediated by the immune system, mainly affecting the sacroiliac joint, and gradually leading to fibrosis of the spinal joint, until new bone formation occurs, resulting in bone rigidity and deformity. The main goals of current treatment are inhibiting new bone formation and delaying imaging progress. In this paper, the mechanism and treatment of new bone formation in AS are summarized and analyzed.

2 Mechanism of new bone formation in AS

The currently known mechanisms of new bone formation mainly include Wnt signaling pathway and BMP signaling pathway. Wnt signaling pathway is currently known as a classic signaling pathway of new bone formation, mainly promoting new bone formation in AS through the transformation of mesenchymal cells into osteoblasts. This signaling pathway includes three intracellular signaling pathways, namely Wnt/ β -catenin signaling pathway, Wnt/ Ca^{2+} signaling pathway, Wnt/planar cell polarity signaling pathway^[1], mainly completed with low density lipoprotein receptor related protein 5 (LRP-5), frizzleds (Fzd), and β -catenin. Fzd receptors that bind to Wnt act on β -catenin inhibit its degradation and phosphorylation, thereby activating the process of new bone formation. The bone morphogenetic protein (BMP) signaling pathway mainly plays a role in the early stages of new bone formation and interacts with Wnt signaling pathway^[2]. Research has shown that the activated BMP signaling pathway stimulates fibroblast differentiation into osteoblasts, which is related to the ossification mechanism of AS^[3]. In the signaling pathway of new bone formation in AS, tumor necrosis factor α (TNF- α), interleukin 1 β (IL-1 β), interleukin (IL-17), and serotonin play key roles.

3 Effect of different treatment schemes on the formation of new bone in AS

3.1 Treatment of new bone formation in AS by combining traditional Chinese medicine In AS, inflammation of the tendon end is closely related to the formation of new bones in AS patients, mainly inducing abnormal upregulation of calcium-sensing receptors (CaSR) and CaSR-PLC γ signal activation in osteoblasts to affect new bone formation through various inflammatory cytokines^[4]. The research on treatment for new bone formation by traditional Chinese medicine mainly focuses on reducing inflammation at the tendon end of AS, and comparing erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), TNF- α , and inflammatory factors such as IL-6, IL-17, and IL-27. The combination of celecoxib and traditional Chinese medicine therapy for treating AS patients with kidney deficiency and Du cold syndrome significantly reduces ESR and CRP levels compared to the simple use of celecoxib capsules group, effectively reduces joint pain, and improves mobility of spinal joint^[5]. Du meridian moxibustion can effectively reduce inflammatory response indicators such as CRP, ESR, TNF- α , IL-17, *etc.*, and regulate the immune imbalance status of AS patients, thereby effectively controlling disease development^[6].

3.2 Treatment of new bone formation in AS by drugs

3.2.1 Non-steroidal drugs (NSAIDs). Some NSAIDs can effectively improve the imaging progression of AS, and the inhibitory effect of NSAIDs on new bone formation is positively correlated with the dosage^[7]. In an RCT study of 215 patients, it was found that patients who received continuous non-steroidal drug treatment had reduced imaging progression at 2 years compared with the on-demand treatment group^[8].

3.2.2 Traditional synthetic DMARDs. Methotrexate can affect Wnt/ β -catenin signaling pathway, and reduce serum DKK-1 level, thereby inhibiting new bone formation^[9]. Sulfasalazine can inhibit the glutamate signaling system, which is beneficial for treating AS peripheral arthritis and inhibiting new bone formation^[10]. Hydroxychloroquine can reduce the transformation of mesenchymal cells into osteoblasts, thereby inhibiting new bone formation^[11]. Cyclophosphamide can damage osteoblast DNA, and inhibit osteoblast function, thereby reducing new bone formation^[12].

Tripterine, the effective component of *Tripterygium wilfordii*, *Tripterygium wilfordii* red pigment, can reduce the expression of intra-articular TNF- α and IL-1, effectively control inflammation, and reduce bone destruction^[13].

3.2.3 Biological DMARDs. (i) TNF inhibitors. TNF inhibitors mainly include etanercept, adalimumab, infliximab, and golimumab. The latest research also confirms that TNF inhibitors can inhibit the radiological progression of AS patients. Long-term (>2 years) use of TNF inhibitors can slow down structural progression or bone proliferation, resulting in a 50% reduction in radiological progression. Of course, the bone proliferation rate of AS patients who used TNF inhibitors gradually decreased in 6 and 8 years when compared with long-term use of 4 years^[14]. Maksymowych *et al.*^[15] used TNF inhibitor (etanercept) to treat AS patients, and the imaging scores of sacroiliac joint and spinal MRI significant reduced at 12 weeks.

(ii) IL-17 inhibitors. IL-17 is closely related to osteoblast formation and new bone formation^[16]. IL-17A regulates osteoblast activity and differentiation through Janus kinase 2 (JAK2) signaling pathway^[17]. IL-17 levels in serum and synovial fluid of active AS patients are elevated^[18]. Secukinumab is an IL-17A inhibitory monoclonal antibody, which can block the expression of IL-17 and prevent the interaction between IL-17 and receptors on the surface of osteoblasts^[19].

In addition, IL-23 inhibitor is a new and promising selective target for the treatment of AS^[20], but its impact on new bone formation in AS still needs further research, and representative drugs contain tildrazumab, risankizumab, and guselkumab. JAK inhibitor upadacitinib is effective and well tolerated in AS patients with insufficient response to NSAIDs^[21]. However, further research is needed on the effects of IL-23 inhibitors and JAK inhibitors on the formation of new bones in AS.

4 Conclusion

AS is a chronic inflammatory spinal arthropathy. As the condition progresses, it leads to ossification of the spine and joints, and new bone formation is an important cause of limited mobility and even disability in AS patients. The early manifestation of AS disease is an increase in inflammatory effects, with a large number of inflammatory cytokines activated, promoting osteoclast activity increase. In the later stages of the disease, the inflammatory effect decreases, leading to an increase in osteoblast activity and the formation of new bones. So far, the mechanism of new bone formation in AS patients has not been thoroughly studied, and there may be factors that influence each other among various signaling pathways. In future treatment, it can continuously explore the treatment plans of traditional Chinese and Western medicine and study the relevant molecular mechanisms of new bone formation in AS, providing more favorable evidence for the treatment of new bone formation in AS with traditional Chinese and Western medicine, and reducing the troubles caused by new bone formation for AS patients.

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