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REVIEW

CURRENT TREATMENT APPROACHES IN ANKYLOSING SPONDILITIS

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ABSTRACT

Ankylosing spondylitis (AS) is a multifactorial rheumatic disease. In today's developing treatment conditions, Non-steroidal anti-inflammatory corticosteroid injections, tumor necrosis factor alpha inhibitors, and disease-modifying antirheumatic drugs offer solutions to patients. In addition to traditional treatments, the effects of nutrition and exercise on ankylosing spondylitis are still being investigated. Genetic factors are also effective on ankylosing spondylitis and are among the factors that should not be forgotten. In this review, we wanted to contribute to the literature by explaining the treatment options that have developed in recent years and the factors affecting the disease.

Keywords: Arthritis, treatment, spondylitis

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic, systemic, inflammatory disease of unknown cause, with a worldwide prevalence of up to 0.9%, which characteristically affects the spine, sacroiliac joint, enthesis, and in some patients, joints other than the axial skeleton (1). The calculation of the Bath AS Activity Index (BASDAI) is widely used to evaluate the activity of the disease (2). This index is based on the assessment and scoring of 6 criteria related to the axial skeleton, peripheral joints, systemic symptoms, and morning stiffness by the patient using a visual analog scale (2). It is known that AS is mostly seen in young men and first appears with symptoms of sacroiliitis (1). Approximately 9/10 patients are found to be positive for the *HLA-B27* gene. However, it is thought that there is no significant difference in the progression of the disease between patients with and without the *HLA-B27* gene (3).

Treatment is generally symptomatic, as a therapeutic approach to address the underlying cause of inflammation in Ankylosing spondylitis is currently not possible. The main purpose of treatment is minimizing pain and preventing morning stiffness and deformities as much as possible. Protecting the posture, physical appearance, and psychosocial health of patients from the effects of the disease is also important (2). Although non-steroidal anti-inflammatory drugs (NSAIDs) are the gold standard in treatment, they are symptomatic treatment options rather than curative (3). Sulfasalazine (SSZ) is a second-line therapy and positive results have been observed in patients with peripheral arthritis (4). Although methotrexate has been found useful in some studies, this has not been proved in controlled studies (1). On the other hand, biological agents have gone beyond symptomatic improvement and become the prominent option in the treatment of the disease in recent years (4). Anti-tumor necrosis factor-alpha (anti-TNF-α) agents target the inflammation mechanism of the disease (1). Treatment with these agents resulted in rapid and significant improvement in the clinical course and laboratory findings in placebo-controlled studies (3). It has been observed that serum vitamin D levels in

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patients with AS are lower than healthy individuals (4). Vitamin D, which has been evaluated as a hormone in recent years, is thought to have a regulatory function on the immune system as well as its role in Calcium - Phosphorus metabolism and bone mineralization (5). This raises the question of how vitamin D plays a role in the progression of AS rather than in the etiology of the disease (5). In addition to medical treatment options, physical exercise is just as important as medical treatment (4). Strengthening the muscles, maintaining the posture, and minimizing the feeling of stiffness increase the patient's quality of life and slow the progression of the disease (3).

REVIEW

Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory are the first-line drugs in all symptomatic AS patients unless it is contraindicated (3). Patients whose symptoms persist despite NSAID therapy are candidates for transition to other treatments (4). This includes cases where at least two different NSAIDs have been used at the maximum recommended dose for at least two weeks, but the disease has not regressed, or the patient has had side effects from the treatment (4).

The aim of NSAIDs is to reduce pain and inflammation by inhibiting the cyclooxygenase enzyme (COX). According to the selectivity of COX-1 and COX-2 isoenzymes, NSAIDs are grouped as traditional NSAIDs (ibuprofen, ketoprofen, indomethacin, naproxen, etc.), and specific COX-2 inhibitors NSAIDs (rofecoxib, celecoxib, etc.) (5). Non-selective and specific COX-2 inhibitor NSAIDs are the most effective treatment group, but it would be beneficial to prefer low-dose NSAIDs due to the observed adverse effects on gastrointestinal, renal, and cardiovascular systems (5). On the other hand, the highest dose (150 mg diclofenac sodium) is preferred by experts for the treatment to be useful (4). As a result of much important evidence, it was seen that all groups of NSAIDs had similar effects and benefits, and that there was a significant difference compared to the placebo group at three months of use (5). In a study evaluating the compliance rates of patients to drugs, it was found that the compliance rates of the patients were 53% to NSAIDs, 65-70% to steroids, and 60-100% to disease-modifying anti-rheumatic drugs (DMARDs), respectively (6). Patients were more nonadherent to NSAIDs than steroids and DMARDs (6). The most common causes of non-compliance were thoughts on the drugs' side effects such as organ failures, gastrointestinal tract damages, and forgetfulness (7). The most common factors that ensured compliance in patients were fears of exacerbation of the disease, reduction of symptoms, and expected side effects (7). When remission is analyzed in AS, it has been proven that NSAIDs provide remission at a rate of 9-35%, reduce mortality, and regress in radiological progression (7). The use of NSAIDs is recommended if medically necessary (8). When the treatment protocols were examined in a study conducted on 23 patients, it was determined that 3.8% of the patients were not receiving treatment, 16.8% were only using NSAIDs, 65.4% were receiving single DMARD, 6.6% were receiving dual DMARD (SSZ + Methotrexate + NSAID), and 7.4% were treated with a biologic agent (anti-TNF-α + NSAIDs) (8).

Corticosteroid Therapy

Systemic glucocorticoids have no place in the treatment of AS. However, short-term medium/high-dose glucocorticoids can be used in patients with axial involvement. Injection therapy of glucocorticoids is recommended in areas of local inflammation in the musculoskeletal system and can be preferred especially in patients with sacroiliitis who have axial pain (6). A randomized double-blind placebo-controlled study investigated the efficacy of two different oral doses of prednisolone (20 and 50 mg/day) versus the placebo group and showed that the short-term efficacy of 50 mg oral prednisolone was superior to the placebo group (8). Another study on steroid usage evaluated the safety and efficacy of slow-release prednisone in 41 patients with AS according to the Assessment in SpondyloArthritis International Society classification criteria (9). According to the results of the study, after three months of treatment with 5 mg of prednisolone at night, significant reductions in spinal and peripheral pain, morning stiffness, and acute phase reactants levels were observed (7, 8).

TNF-alpha Inhibitor Therapy

Tumor necrosis factor (TNF) has an important role in many inflammatory diseases (9). TNF has two forms as alpha and beta and binds to TNF 1 and 2 receptors in the cell nucleus (9). It is produced by macrophages, then destroyed and converted to its soluble form (9). This form causes an inflammatory and immune response in the cell by initiating the release of many cytokines and apoptosis pathways (9, 10).

The use of anti-TNF-α drugs in patients who did not respond to conventional treatment has revealed dramatic results (11). Anti-TNF-α samples approved by the United States Food and Drug Administration for use in the treatment of AS are infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol (11). These anti-TNFα agents can be preferred as second-line therapy in patients who have not benefited sufficiently from NSAIDs (11). Clinically and radiologically significant curative effects of anti-TNF-α were detected in patients with AS (10). With this treatment, inflammation in the axial skeleton was decreased, and satisfactory results were observed in Bath Ankylosing Spondylitis Functional Index (BASFI) and BASDAI scores (12).

In a study of 133 patients treated with NSAIDs and SSZ in Republic of Korea, the treatment results of 69 patients were very successful, and the treatment was not changed (group A). Low back pain persisted in the remaining 64 patients, and their treatment was arranged as anti-TNF-α (group B) (12). When the patients and their radiological parameters were followed for six months, BASDAI, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were evaluated clinically, and significantly more lumbar lordosis was detected in patients in

group B compared to patients in group A. Although no significant difference was observed in other radiological parameters, clinically, patients in group B showed more positive results in ESR, CRP, and BASDAI scores than in group A (13).

In a study conducted in China, 39 patients treated with etanercept and 41 patients treated with infliximab were evaluated for treatment efficacy at 12 and 24 weeks. Clinically, both drugs appeared to have positive effects on the Schober test, morning stiffness, and BASDAI and BASFI scores (14).

Since the side effects of anti-TNF-α drugs are mostly mild, changing the treatment is usually not required. However, dangerous side effects such as severe infection can be observed (11). More than 10% of patients have headaches, injection site reactions, and infusion reactions (11). In addition, anemia, mild elevation in liver function tests, upper respiratory tract infection, and geographic information system problems may occur (10).

Disease-modifying Anti-rheumatic Drug Therapy

Disease-modifying anti-rheumatic drugs are popular in the treatment of patients with AS because they are beneficial in peripheral rather than axial symptoms (15). SSZ is a synthetic drug formed by the bonding of sulphapyridine, a sulfonamide derivative, and a 5-aminosalicylate, an anti-inflammatory salicylate derivative, with an azo bond (16). The efficacy of this drug has been recognized, especially in HLA-B27-positive arthropathies (16). They can be used for therapeutic purposes and to prevent anterior uveitis in patients with early stages of the disease, elevated erythrocyte sedimentation rate, and peripheral arthritis (15). The most common side effects of SSZ include acute hemolytic anemia, leukopenia, thrombocytopenia, nausea, vomiting, rash, and fever (16).

In a randomized controlled study conducted by Khanna Sharma et al. (16), the study group was started with 500 mg of SSZ twice a day and this amount was increased by 500 mg per week to the target dose of 2 g/day. The control group was given a similar-looking placebo. The total duration of treatment in this study was six months. Comparing the mean change in BASDAI scores at six months follow-up, 61.3% of patients in the treatment group had at least 50% (17). In the study, when the mean changes in disease activity were evaluated based on the AS Disease Activity Score, BASDAI, and, Bath AS Metrology Index (BASMI), it was observed that there was a betterment of 80% (17). As the second-line therapy after NSAIDs, SSZ additionally can reduce systemic inflammation and mediate reduction of cardiac risk (17). Another study investigated whether cardiovascular disease was the primary cause of death in patients with AS. In this 10-year population-based case-control study, in which 3,766 AS patients with coronary artery disease were included as the control group, coronary artery disease developed in 8.4% of AS patients (18). According to the results of the study, it was shown that the use of SSZ at an average dose of 0.5 mg/day was negatively associated with the development of coronary artery disease in patients with AS (18). In addition, a positive correlation was found. A group of researchers declared that lumber spine Bath AS Radiology Index scores in AS patients without polymorphonuclear leukocytes showed a lower degree of sacroiliitis (19). They also included sulfasalazine in their studies and had positive results at the end of 4 months. It has been observed that SSZs reduce the transcription of HLA-B27 by decreasing the levels of IFNγ, interleukin-17, and TNF-α. However, although the disease progression could be improved with this treatment, it did not reverse the spinal damage (20).

Janus Kinase inhibitors have just joined the treatment of AS. They belong to the group of DMARDs (20). They are considered disease-modifying because they reduce the progression of damage in the joints (20).

Interleukin-17 inhibitors such as secukinumab have started to be used in the treatment of AS (20). In addition to having a pronounced effect on patient recovery, they also slow down the damage caused by the disease (20).

Exercise

Chronic inflammatory diseases that primarily affect the joints and musculoskeletal system, such as AS, cause functional damage because of joint destruction, comorbid conditions, and side effects of drugs over time (20). Despite the developments in pharmacological treatments in recent years, a permanent solution has not been found yet for the functional losses and the deterioration in the quality of life caused by rheumatic diseases (20). For this reason, it is recommended to do exercises related to the joint and muscle group involved, in addition to drug treatment, to slow down the progression of the disease and protect their functional capacities (20). In order to adapt to the planned exercise program for the patient, it should initially be done under the supervision of a physician (21). In the following periods, patients' lifelong participation in exercise should be ensured by admonishing the participation of relatives and starting to see the results of physical rehabilitation (21).

It was obtained that home exercise for 30 minutes a day, at least 5 days a week, can slow progression of the disease (20). However, outcomes related to the quality of life are controversial (20, 21). It was observed that the aerobic capacity of patients with AS was lower than healthy people, and it was found to be directly correlated with the impairment of physical condition (21). Another study conducted in Turkey showed the benefit of adding aerobic exercise to conventional exercise on physical capacity (22). When aerobic exercise training is together with clinical pilates exercises, it reduces disease activity, but increases spinal mobility upper extremity flexibility, dynamic balance, forced vital capacity, quality of life, and fatigue severity (22). It was also concluded that restrictive type respiratory failure and emerging insufficiency in patients with AS can be prevented by correct and effective exercise (23).

Nutrition

Although recent studies suggest that there may be a relationship between AS and intestinal microflora, no clear evidence has been obtained from the studies (24). In a control group study in which probiotics were used, it was observed that the probiotics cause a decrease in inflammation values, and BASDAI and BASFI scores, but it did not create a statistically significant result that would provide definitive information (24).

Smoking is also a factor that reduces the life comfort of AS patients. The underlying reason for this decline is that smoking drastically changes the stage and progression of the disease. At the same time, a relationship between smoking and syndesmophyte formation has been demonstrated by magnetic resonance imaging. Eventually, it has been observed that AS is not directly related to nutrition, except for these two nuances. Several studies on the subject are ongoing. Vitamin D, an anti-inflammatory and immune modulatory hormone, regulates bone metabolism by playing a role in calcium and phosphorus metabolism (25). The relationship between AS and vitamin D is a subject of studies since vitamin D manifests itself in AS in case of deficiency (25). In conclusion, vitamin D is seen as an important parameter in the treatment approach and follow-up of patients with AS, and its replacement should be performed if necessary (25).

DISCUSSION

Although the negative effects of high-dose NSAID use on the gastrointestinal, cardiovascular, and renal systems were reviewed in a study, it was concluded that high doses of NSAIDs (150 mg diclofenac sodium) should be used in the treatment of AS and it was found beneficial in this review article (7). Despite the results that corticosteroid treatment did not make a significant difference for AS, there is a study in which 50 mg prednisolone was used for AS treatment and it was effective (15). Another treatment option, SSZs, may become the primary treatment for other patients with predominant peripheral symptoms (16). However, the report of a larger randomized controlled trial showing that this drug provided significant improvement in rheumatologic patients with peripheral joint involvement failed to show a similar outcome in AS patients (26). Son et al. (12) stated that after a 5-year period, anti-TNF-α did not have significant radiological effects. However, in this review, it is clear that anti-TNF-α has positive effects radiologically, especially on lumbar lordosis. We concluded that anti-TNF-α drugs are more effective than other drugs in AS patients. Anti-TNF-α agents are important drugs to be preferred in cases that do not respond to conventional treatment, but they are more expensive than other agents (22). However, despite its high cost, it is an effective option for suitable patients due to its better clinical outcomes compared to other agents (26). As a result of the studies we examined, it was understood that the exercise program added to the medical treatment in AS had positive effects on the flexibility, muscle strength, and aerobic capacity of the person (20). However, in the reviewed systematic review of Soy Buğdaycı and Paker (19), it was mentioned that the effects on pain, stiffness, and increased quality of life are low. In addition to exercise, there are studies on the relationship between AS and nutrition, in which smoking significantly worsens the course of the disease, and probiotics and vitamin D have positive effects on the musculoskeletal system (25). However, meaningful statistics could not be reached that would provide definitive information (24, 25).

CONCLUSION

In today's developing treatment conditions, non steroidal anti inflammatory drugs, corticosteroid injections, tumor necrosis factor alpha inhibitors and disease-modifying antirheumatic drugs offer solutions to patients. In addition to traditional treatments, the effects of nutrition and exercise on AS are still being investigated. Genetic factors are also effective on AS and are among the factors that should not be forgotten. In this review, we wanted to contribute to the literature by explaining the treatment options that have developed in recent years and the factors affecting the disease. Treatments in AS are various, therefore every patient should be cared with a multidisciplinary approach.

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