

Treatment of ankylosing spondylitis

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Abstract: Ankylosing spondylitis is a chronic, inflammatory, rheumatic disease that can reduce the quality of life and increase the risk of disability and mortality. It also causes direct and indirect economic losses due to health expenses and as a result of workforce loss. Management of this disease consists of pharmacological and nonpharmacological modalities. Until recently, pharmacological treatment options have been very limited. However, development of novel biological drugs revolutionized the management of this disease. The aim of this review article is to present an updated overview of the pharmacologic treatment of ankylosing spondylitis. Nonpharmacological treatment modalities including physiotherapy and exercise are only briefly mentioned and surgical treatment is not discussed.

Key words: Ankylosing spondylitis, treatment, nonsteroid antiinflammatory drugs, disease modifying antirheumatic drugs, corticosteroids, anti-TNF agents

1. Introduction

Ankylosing spondylitis (AS) is a chronic, inflammatory, rheumatic disease involving primarily the spine and sacroiliac joints. It is a prototype of spondyloarthritis (SpA) group diseases and its prevalence in Turkey has been reported as 0.49% (1). It is encountered in mostly young adults and in 80% of the cases symptoms appear before 30 years of age (2). Studies have revealed that the quality of life is reduced and the risk of disability and mortality is increased in patients with AS (3,4). It has been reported that the direct (due to health expenses) and indirect (as a result of workforce loss) economic losses associated with the disease are similar to those of rheumatoid arthritis (RA) in the long term (5).

Management of AS consists of pharmacological and nonpharmacological treatment modalities (6–11). The pharmacological treatment options are limited; however, with the recent introduction of biological drugs, remarkable improvements have been reported in this field. In general, the treatment targets include control of symptoms and inflammation (pain, stiffness, and joint swelling), preservation/normalization of physical function, prevention of progressive structural damage and disabilities, and eventually maximizing the long-term health-related quality of life (6,11). The aim of this review article is to present an updated overview of the

pharmacologic treatment of AS, as defined by the modified New York criteria (Table 1) (12). Nonpharmacological treatment modalities including physiotherapy and exercise are only briefly mentioned and surgical treatment is not discussed.

2. Nonpharmacological treatment approaches: physiotherapy and exercise

The nonpharmacological treatment for AS comprises patient training and regular exercise. Pharmacological treatment and nonpharmacological treatment approaches complement each other. Physiotherapy and exercise for the treatment of AS are also cost-effective (13). A recent Cochrane article summarized the available scientific evidence on the effectiveness of physiotherapy interventions in the management of AS (14). Personal home exercising and training, when compared to AS patients without such interventions, lead to significant improvement in some spinal mobility parameters (finger tips-to-floor distance); however, they have no effect on disease activity, pain, stiffness, and global patient evaluation (14). Studies comparing group physiotherapy programs applied with a supervisor with personal home exercise programs showed that there were no differences among groups in regard to pain, stiffness, and function; however, some spinal mobility parameters (Schober's distance) and patient global

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Table 1. Modified New York criteria for AS (12).

Clinical criteria	
1-	Low back pain and stiffness for longer than 3 months, which improve with exercise, but are not relieved by rest
2-	Restriction of motion of the lumbar spine in both the sagittal and frontal planes
3-	Restriction of chest expansion relative to normal values correlated for age and sex
Radiological criterion	
1-	Sacroiliitis grade ≥ 2 bilaterally, or grade 3–4 unilaterally

Definite ankylosing spondylitis is present if the radiological criterion is associated with at least one clinical criterion

evaluations had a tendency to improve in patients following a group physiotherapy program (14). In the same review article, inpatient spa-exercise therapy followed by group physiotherapy was concluded to be better than group physiotherapy alone (14).

Messages/recommendations:

- Regular exercise program must be started as part of the treatment immediately after the patient is diagnosed.
 - The patient must be thoroughly enlightened about the necessity of nonpharmacological practices in all stages of AS (early or late disease) throughout their lives as part of the treatment.
 - Personal home exercises are more effective than doing no exercise at all.
 - The exercises done under supervision are more effective than home exercises.
 - SpA treatment applied in combination with the group exercise is more effective than group physiotherapy practice.
 - The intensity of exercises must be adapted according to the activity and stage of the disease for each patient.
 - Patients must be trained on physical therapy explaining which posture is appropriate, how they should walk and sleep, and which exercises are suitable.
 - Specific exercises, such as spine extension, joint range of motion, and deep breathing exercises, must be applied a minimum of twice a day.
 - Patients must be instructed for the right postures while walking, sitting, and laying down.
 - They should be advised to walk tall and keep the spine in an upright position as much as possible. They should avoid some unintentional postures, such as spinal curvature or leaning forward while working.
 - Lying down in the face down position for 15–30 min a few times a day may prevent kyphosis and flexion contracture in the hip.
 - Sleeping on a stiff bed with a thin pillow or without may reduce the possibility of developing spinal deformation.
 - Swimming and hydrotherapy are the most effective methods to reach all these physiotherapy targets.
- A cane or a walker may be used for people with severe kyphosis or lower extremity arthritis.
 - Sports supporting axial mobility (swimming, badminton, volleyball, running, skiing, etc.) should be preferred over other sportive activities carrying high bone-fracture risk (cycling, horse riding, boxing, football).

3. Pharmacological treatments in ankylosing spondylitis

3.1. Nonsteroid antiinflammatory drugs

Nonsteroid antiinflammatory drugs (NSAIDs), both nonselective and cyclooxygenase (COX)-2-specific inhibitors (Coxibs), are currently the first-line treatment for AS. Efficacy of NSAIDs on AS was assessed in various randomized controlled trials (RCTs) and they were found superior as compared to placebos (15–23). NSAIDs improve spinal pain, morning stiffness, and function (15–17,19,23). They significantly reduce peripheral joint pain (20) and enthesal pain (21,22) and also acute phase protein levels (23,24). Their efficacy is partly dose-dependent (19). Most patients describe significant improvement in their low back pain and stiffness within 48 h after a full dose of NSAID (19), but clinical findings reappear within 2 days following their withdrawal (16,25,26). When patients were asked about the level of their response to NSAID treatment in a cross-sectional survey, 70%–80% of them reported that they had good or very good symptom relief (19,23,27). However, this level of response is obtained in only 15% of patients with mechanical spinal pain (27). Therefore, a good response to NSAID treatment is used as a diagnostic criterion for distinguishing inflammatory back pain from mechanical back pain (27). On the other hand, lack of response to NSAID treatment is considered as a bad prognostic factor (28). Many studies comparing the efficacy of different NSAIDs showed no difference in their effectiveness in the treatment of AS (15,17,20,29). COX-2-inhibitors are also as effective as conventional NSAIDs to reduce spinal pain and preserve function in AS (15,16,18,19). One of the questions for which an answer is sought in clinical practice is how to decide on the dose of the NSAID to be used. The studies conducted indicate

that the dose adjustment must be made depending on the patients' symptoms. While moderate doses of NSAIDs can be sufficient in some AS patients, in some others maximum tolerated doses must be taken in order to obtain an adequate response (17,23). Dose timing can be experimented with to get the best pain relief for the entire day. Long-acting ones taken at night may be preferred for patients who suffer from night pain and morning stiffness (8). The maximum recommended doses of NSAIDs for the treatment of AS are displayed in Table 2 (30).

Another unresolved issue about the use of NSAIDs is whether they should be taken as needed (on demand) or on a regular (continuous) basis. Regular use of NSAIDs over 1 year demonstrates sustained improvement in pain and function (17,19). Moreover, there is some evidence suggesting that continuous and long-term use of NSAID treatment reduces the radiological progression. An old retrospective study conducted by Boersma et al. including 40 AS patients demonstrated that long-term and regular use of phenylbutazone reduced spinal ossification (31). A recent RCT with celecoxib also showed less radiological progression in patients who used NSAIDs continuously than in those who used them on an on-demand basis (32). A post hoc subgroup analysis of this study revealed that this effect was seen only in the patients with increased C-reactive protein (CRP) levels (33). In the recent German

Spondyloarthritis Inception Cohort (GESPIC), less spinal radiographic progression was observed in AS patients with high NSAID intake. Interestingly, in this study also, this effect was limited to patients with elevated CRP levels (34). Although these results are promising, considering the potential cardiovascular and gastrointestinal risks associated with NSAIDs, we think that the available evidence is not yet sufficient for recommending continuous use of NSAIDs in all AS patients, and until more evidence is available on the effectiveness of NSAIDs in preventing progression of structural damage, patients should be advised to use the lowest effective dose of NSAIDs for the shortest duration consistent with their individual needs in accordance with the recommendations of both the US Food and Drug Administration and the European Medicines Evaluation Agency (35,36).

One of the current issues encountered, especially after the tumor necrosis factor alpha (TNF- α) inhibitors came into clinical use, is the characterization of patients who are resistant to NSAIDs. Normally, reaching the maximum effect of NSAIDs does not take more than 1–2 weeks (19); however, in some cases it might be necessary to use longer periods to determine the optimum dose (approximately 6 weeks) (6,17). Some patients who do not respond to one NSAID may respond to another (37). Therefore, different NSAIDs must be tried at maximum doses. According to French guidelines, failure with NSAID therapy is defined as an inadequate response to at least three NSAIDs at optimal tolerated dosages for 3 consecutive months, in the absence of contraindications (9). NICE also recommends a trial of at least 2 different NSAIDs taken sequentially at maximum tolerated or recommended dosage for 4 weeks before concluding that a patient is resistant to NSAIDs (38). The latest update of ASAS recommendations also requires an adequate therapeutic trial of at least 2 NSAIDs for a minimum of 4 weeks, which is significantly shorter than the previously suggested duration of 3 months, before initiating anti-TNF therapy (39). A patient who has failed NSAID therapy should be considered to start anti-TNF therapy if he has active disease (BASDAI \geq 4) for 4 weeks and a positive expert opinion in favor of biologic therapy (39).

3.1.1. Side effects of NSAIDs

NSAID studies conducted with AS patients are relatively short-term and include limited numbers of patients. Therefore, there were only limited data on the long-term safety of NSAIDs, until the Coxibs were compared to conventional NSAIDs or placebos in long-term studies. Adverse effects associated with the use of NSAIDs in AS patients are similar to those reported in other rheumatic patients (37). The safety profiles of NSAIDs do not seem to differ between long and short half-life agents (17,19,20).

Table 2. Maximum recommended dosage of NSAIDs in patients with AS (30).

NSAID	Maximum recommended dosage (mg)
Diclofenac	150
Naproxen	1000
Aceclofenac	200
Celecoxib	400
Etodolac	600
Etoricoxib	90
Flurbiprofen	200
Phenylbutazone	400
Ibuprofen	2400
Indometacin	150
Ketoprofen	200
Meloxicam	15
Nimesulide	200
Piroxicam	20
Tenoxicam	20

3.1.1.1. Side effects on the cardiovascular system

Although the risk associated with cardiovascular (CV) toxicity was initially reported with rofecoxib (40), further studies revealed that other selective COX-2 inhibitors (41–43) and also conventional NSAIDs had a similar risk, suggesting that it is a class effect of all NSAIDs (44,45). There are various factors that contribute to an individual's CV risk, such as age, history of CV diseases, and the NSAID dose. Serious CV incidents during NSAID treatment were low in young patients with low basal CV risk (43,46,47). On the other hand, the risk of CV incident in AS patients does not change between continuous or on-demand use (32). In addition, both classical NSAIDs and Coxibs may cause or exacerbate hypertension independently from their prothrombotic effects and this may have a negative effect on CV risk (32).

The CV safety of nonselective NSAIDs other than naproxen seems to be similar to that of COX-2-specific NSAIDs other than rofecoxib (48,49). It has been reported that naproxen is the only NSAID associated with neutral CV risk relative to placebos (47). High-dose naproxen (550 mg twice daily) suppresses platelet thromboxane production and therefore inhibits platelet aggregation. This has been suggested to be the underlying mechanism for the observed lower CV risk with naproxen (50). On the other hand, diclofenac has been reported to have the highest CV risk among nonselective NSAIDs, followed by ibuprofen (48,49).

3.1.1.2. Side effects on the gastrointestinal system

Gastrointestinal (GI) system toxicity, which is a well-known side effect of NSAID treatment, is caused by the inhibition of prostaglandin synthesis in the gastric mucosa and also due to some nonprostaglandin effects. Studies indicate that GI event risk increases over time with longer use of NSAIDs (51,52). However, short-term treatment is not risk-free (34). Continuous use of NSAIDs in AS patients confers a greater GI event risk compared to intermittent use (32). NSAID users compared to controls are almost 5.4 times more likely to experience serious GI events, such as upper GI ulcers, bleeding, or perforation, and the risk is generally dose-dependent (53, 54). Although Coxibs have a lower risk for serious GI events than nonselective NSAIDs, they seem to have similar frequency of dyspepsia and similar minor symptoms, which can often cause discomfort in many patients (16,55). Moreover, conventional NSAIDs when used with a proton pump inhibitor, misoprostol, or double-dose H2 receptor blocker display a similar GI toxicity profile to selective COX-2 inhibitors (56,57). Various risk factors have been reported for serious GI complication risks associated with NSAIDs: 60+ years of age, history of ulcer and ulcer complications, simultaneous corticosteroid, anticoagulant drugs or aspirin (325 mg/g) intake, alcohol usage,

smoking, high dose of NSAIDs, taking 2 different NSAIDs simultaneously, and possibly *Helicobacter pylori* infection (58). Mucosal lesions may occur in the postduodenum intestinal areas as a result of use of conventional NSAIDs or Coxibs (59). Current data indicate that use of NSAIDs may be associated with ulcers or ulcer complications in the colon. Exacerbation in inflammatory bowel disease (IBD) and de novo induction of IBD have been reported to occur as a side effect of NSAID therapy (60). However, studies conducted with Coxibs suggest that they are not associated with an increased frequency of IBD exacerbation (10). Moreover, retrospective case-control studies with classical NSAIDs also showed no increase in occurrence of IBD exacerbation (10).

Messages/recommendations:

- NSAIDs improve spinal pain, morning stiffness, and function, and additionally they have positive effects on joint pain and enthesal pain. Therefore, they should be used as the first-line treatment in AS.
- Treatment must be started with the maximum dose and the dosage should be adjusted based on patient response and tolerance. Patients do not need to take NSAIDs if they have no symptoms.
- No differences in efficacy are evident between different NSAIDs including conventional NSAIDs and Coxibs. Therefore, choice of NSAID should be based on consideration of potential risks for side effects, cost, dosing intervals (less frequent use of drugs increases compliance), individual response, and possible drug interactions.
- Long-acting night doses can be used in patients suffering from night pain and morning stiffness.
- Combined use of NSAIDs should be avoided as it will increase the risk of GI toxicity with usually no additional benefit on symptom relief.
- In patients with high CV risk, naproxen should be preferred.
- In patients with a high risk for GI toxicity, a Cox-2 selective agent or a traditional NSAID in combination with a gastroprotective agent (i.e. PPI) should be considered.
- In patients with active AS and coexistent IBD, NSAID treatment can be used if IBD is not active.

3.2. Disease-modifying antirheumatic drugs

First, we would like to state that the term 'disease-modifying antirheumatic drugs' (DMARDs) has been borrowed from RA to refer to the category of drugs that suppress synovial inflammation and prevent structural damage in that disease; however, to date, none of them has been proven to have any 'disease-modifying' effects in AS (61). Sulfasalazine (SSZ) is the most frequently studied disease-modifying drug in the treatment of AS. The therapeutic efficacy of SSZ for the treatment of AS was addressed in

two metaanalyses (62,63). The first metaanalysis found that SSZ significantly improved severity of pain, duration of morning stiffness, severity of morning stiffness, general well-being, and erythrocyte sedimentation rate (ESR) compared with a placebo in AS (62). In a subsequent more extensive metaanalysis, 11 studies including 895 patients (disease duration: 3.8–20 years) were evaluated. In these studies, patients used 2–3 g/day of SSZ (for 12 weeks to 3 years). In this metaanalysis no differences were found between the SSZ and placebo groups in axial pain, spinal mobility, enthesitis, and patient or physician global assessment. However, there was a significant difference between SSZ and placebo in the severity of morning stiffness (1.4 units; VAS, 0–10) and ESR (4.8 mm/h) in favor of SSZ (63). In this metaanalysis, the authors concluded that the patients with early disease, high ESR (active), and peripheral involvement might benefit from SSZ treatment (63). A RCT has shown that the severity and the frequency of acute anterior uveitis (AAU) attacks were decreased in AS patients taking SSZ (64). This was supported by a subsequent retrospective study, which reported a lower prevalence of AAU in patients on SSZ treatment (65). Studies have not shown any effectiveness of SSZ on dactylitis scores and enthesopathy index (63,66,67). In a 1-year double-blind placebo-controlled trial including 40 patients, no effect of SSZ was observed on radiological progression as measured either by plain X-ray or computerized tomography (68).

Efficacy of methotrexate (MTX) in AS has been investigated in a number of studies, including three controlled studies (7.5–10 mg/week, oral use, and study period of ≤ 12 months) (69–71), which were reviewed in two metaanalyses (72,73). In a 3-year open study that included 17 patients, low-dose MTX demonstrated a positive effect on night pain, general wellness, ESR and CRP levels, and some other parameters like Schober's and occiput-to-wall distance, and it also significantly reduced the need for NSAID use over time. Moreover, radiographs of the spine and sacroiliac joints did not show any signs of disease progression over the study period (74). In an open study in which MTX at 12.5 mg/week was administered subcutaneously (SC) for 1 year, no effect was observed on axial symptoms such as spinal pain, morning stiffness, and spinal movements; however, it was of note that no uveitis attack occurred during the study, and the frequency of peripheral arthritis was significantly reduced (75). In a recent open study, 20 active AS patients were treated with MTX at 20 mg/week SC for 16 weeks. No change was detected between baseline and week 16 for mean BASDAI score or for any other clinical parameter or CRP; only a small but nonsignificant decrease was observed in the number of swollen joints. (76). MTX was compared with naproxen in one RCT (69) and with a placebo in two

others (70,71). In a single-blind study lasting 12 months, the efficacy of MTX 7.5 mg/week + naproxen was not found to be superior to naproxen alone (69). In a 6-month RCT with relatively fewer patients with active AS, no difference was observed in changes of Bath Ankylosing Spondylitis Functional Index (BASFI), BASDAI, and Bath Ankylosing Spondylitis Metrology Index (BASMI) scores and CRP levels in patients receiving MTX compared with those receiving a placebo, including in the subgroup of patients with peripheral arthritis (71). In another RCT comparing MTX with a placebo, a higher response rate was obtained as measured by a composite index based on the BASFI, BASDAI, severity of morning stiffness, patient and physician global evaluation, physical wellness, and health assessment questionnaire for SpA (70), but this benefit was revealed to be questionable after further analysis (77). Two metaanalyses reviewing the published controlled studies did not find evidence that MTX was beneficial in patients with AS (72,73). However, the studies included in the metaanalyses had small sample sizes, were of short duration, and used relatively low doses of MTX. ASAS/EULAR recommendations also confirm that there is no evidence for the effectiveness of MTX in AS (6,11).

There are only two small studies evaluating the efficacy of leflunomide (LEF) in the treatment of AS (78,79). The first study was an open-label trial lasting 6 months, which included 20 patients with active AS who used a daily dose of 20 mg of LEF after a loading dose (78). No improvement was observed in clinical outcomes including BASDAI, BASFI, BASMI, patient and physician global assessments, quality of life (short form-36), global pain, and CRP. However, mean number of arthritic joints decreased significantly by week 12 in patients with peripheral arthritis and the improvement remained significant until the end of the study. The second study was a 24-week double-blind randomized controlled study, in which 45 patients with active AS were randomized to either LEF at 20 mg daily or a placebo (79). At the end of the study, the percentage of ASAS20 responders (the primary endpoint) was not significantly different between the LEF and placebo groups. No significant differences were seen in other clinical assessment outcomes, either, such as general well-being, metrology index, swollen joint count, ESR, and CRP (79).

Based on the available data, which do not provide any evidence for the efficacy of SSZ or any other DMARDs on axial symptoms, French recommendations for pharmacotherapy (excluding biotherapies) for AS do not recommend the use of SSZ, MTX, or LEF to treat the axial manifestations of AS, but do suggest a possible role for the use of SSZ in patients with peripheral arthritis (8). ASAS/EULAR recommendations also confirm the lack of evidence for the efficacy of DMARDs, including

sulfasalazine and methotrexate, for the treatment of axial disease, and suggest considering a therapeutic trial of SSZ in patients with peripheral arthritis (80).

Messages/recommendations:

- Despite the lack of evidence for the effectiveness of SSZ on the axial symptoms of AS, some rheumatologists still use this agent in pure axial disease, based on their personal experience.
- SSZ (2–3 g/day) can be used in patients with peripheral arthritis. It has no beneficial effect on peripheral symptoms such as dactylitis and enthesitis.
- The available limited data suggest that neither MTX nor LEF shows any beneficial effect in treating axial or peripheral symptoms of AS.
- In patients experiencing AAU attacks, SSZ treatment should be considered.

3.3. Corticosteroids

There are very limited data on the use of glucocorticosteroids (GCs) in patients with AS. Although controlled studies on the effects of low-dose GCs in AS are lacking, some experts suggest that systemic GCs, when applied in low and moderate dosages, are not effective in treatment of symptoms of AS (81,82). However, a recent small RCT suggests that 2 weeks of high-dose oral prednisone produces a clinically meaningful response in patients with active AS (83). In this study, AS patients refractory to NSAIDs were randomized to receive either prednisolone at 20 mg or 50 mg or a placebo, once daily for a 2-week period. Although the primary endpoint of the study, BASDAI50 at week 2, did not reach statistical significance (33%, 27%, and 8% in patients taking prednisolone at 50 mg/day, prednisolone at 20 mg/day, and placebo, respectively), the mean improvement of BASDAI score in the 50 mg prednisolone group was significantly higher than in the placebo group. The change in the 20 mg group was not different than in the placebo group (83).

Three small uncontrolled studies conducted on AS patients with intravenous (IV) pulse GC therapy all reported favorable results (84–86). In these studies, pulse GC therapy, which was administered in a dose of 1000 mg of IV methylprednisolone daily for 1 to 4 days, produced clinically relevant response starting in days and lasting for months (84–86). A subsequent RCT by Peters et. al., which compared 375 mg and 1000 mg doses of methylprednisolone, found no difference between the two doses for pain, morning stiffness, and spinal mobility measurements; however, both doses were effective in improving these outcome measures compared to baseline (87). According to the French guidelines, the use of systemic GC in AS is not recommended except in specific circumstances (e.g., pregnancy) (8). ASAS/EULAR recommendations also advise against the use of systemic GC therapy for axial symptoms of AS (11).

Despite the lack of controlled data regarding efficacy of local GC injections for enthesitis and hip or peripheral arthritis, GC injections to local sites may be advisable in patients with AS, according to expert opinion (8). Effectiveness of GC injections into the sacroiliac joints was assessed in open and controlled studies (88–92). In two placebo-controlled RCTs, GC injections into the sacroiliac joints elicited significantly better pain control compared to a placebo or a local anesthetic, and this effect continued for 2 to 6 months (90,91). Better results have been reported with imaging-guided injections (such as CT or ultrasound) than with blinded interventions (90,93).

Messages/recommendations:

- Systemic use of GC treatments must be avoided in the treatment of AS. Their use should be limited to situations such as pregnancy and when other available treatments are contraindicated.
- Imaging-guided GC injections into the sacroiliac joints may be considered in patients suffering from predominantly sacroiliac pain despite the use of NSAIDs at optimum doses.
- Patients with resistant enthesitis, peripheral arthritis, or hip arthritis may benefit from intraarticular or local GC injections.

3.4. Anti-TNF agents

Following the elucidation of the role of TNF- α in the pathogenesis of AS (94), TNF inhibitors have been effectively used for the treatment of AS and have revolutionized the management of this disease, for which there had previously been very limited treatment options. Infliximab (INF), etanercept (ETA), adalimumab (ADA), and golimumab (GOL) are the currently available TNF inhibitors in Turkey, which have been approved for the treatment of AS.

3.4.1. Efficacy

INF, a human-mouse chimeric monoclonal anti-TNF- α antibody, was the first biological drug tested in a RCT for the treatment of AS (95). This first study and many other subsequent placebo-controlled RCTs have demonstrated that INF is effective in treating axial and peripheral symptoms of AS, including enthesal involvement (95–97). Favorable effects have also been obtained on quality of life, spinal mobility, and CRP levels with the use of INF (95–97). INF has a rapid onset of action and the response is usually evident by the second week of treatment (95). Long-term follow-up data have shown persistent clinical efficacy and safety of over 8 years (98). It is reported that, when INF is discontinued, 90% of patients relapse within 36 weeks, and almost all patients relapse within 1 year (99). However, it has been shown to be safe and effective when readministered after discontinuation (100). In the RCTs of INF in AS, it was usually administered intravenously via infusions of 2 h in duration at a dose

of 5 mg/kg at 0, 2, and 6 weeks followed by 5 mg/kg every 6 weeks thereafter (95,101). A recent metaanalysis compared the safety of the shorter duration infusions of INF (<1 hour) with that of standard 2–3 h infusions and concluded that rapid INF infusions of ≤ 1 h in duration are safe when compared to standard 2- to 3-h infusions in selected patients who previously tolerated three to four standard infusions (102). Some studies suggest that INF may be effective in active axial AS even at doses lower than the standard regimen (103,104). In one study, low-dose INF was found effective also on peripheral symptoms (104). In a recent double-blind study, INF at an IV dose of 3 mg/kg every 8 weeks following a loading dose elicited significantly higher ASAS20 response rates compared to a placebo at week 12 (105). Moreover, in the INF group, significant improvement was observed in measures of function, disease activity, spinal mobility, quality of life, and acute phase reactants (ESR and CRP). During the extension phase of this study, almost 2/3 of patients in the INF group did not achieve the clinical target (50% reduction in BASDAI and a BASDAI of <3) and needed a dose increase (5 mg/kg) by 38 weeks; higher CRP level was a predictor of failure to achieve the defined clinical target. On the other hand, one study showed that SpA patients with persistent disease activity despite receiving a standard dose regimen of INF may benefit from reducing the dose interval to 6 weeks (106). A randomized study compared the continuous and on-demand use of INF and reported higher ASAS20, ASAS40, and partial remission response rates at week 58 with continuous INF treatment (107). In the same study, addition of MTX to on-demand use of an INF regimen did not have a significant effect on patient response. Another French group published two studies that also showed no effect of MTX on serum concentrations of INF, BASDAI scores, and biomarkers of inflammation (108,109).

ETA is a human fusion protein with dimeric structure. It is composed of two human p75 TNF receptors bound to an Fc fragment of immunoglobulin (Ig) G1. It binds to the TNF receptor and lymphotoxin-alpha with high affinity. The efficacy of ETA in AS has been demonstrated in several placebo-controlled trials (110–113). ETA has been shown to be effective not only on axial symptoms of AS, but also on peripheral symptoms, such as arthritis and enthesitis (114,115), and has been found more effective than SSZ on all joint assessments in patients with AS and peripheral joint involvement (115). Clinical efficacy and safety of ETA have held up in patients with active AS having been followed for as long as 7 years (116). ETA was administered at a twice weekly dosage of 25 mg during initial studies but is now most commonly prescribed at a weekly dose of 50 mg, since this dose regimen was demonstrated to be equally effective in a RCT (117,118). A higher dose of

ETA (100 mg/week) has been reported to be as safe as the standard dose (50 mg/week); however, it does not increase the efficacy significantly (119). Discontinuation of ETA results in exacerbation of AS in the majority patients; however, no reduction in efficacy is observed when treatment is reinitiated with ETA (120). The effect of ETA in patients with advanced AS was studied in a placebo-controlled double-blind randomized study, which showed significant improvement in pain, disease activity, function, spinal mobility, and CRP, as well as in pulmonary forced vital capacity measurements (121,122).

ADA is a fully humanized antibody against TNF- α . The recommended dose for adult patients with AS is 40 mg administered SC every other week. The effectiveness of ADA in improving axial symptoms of AS, as well as mobility, peripheral arthritis, enthesitis, quality of life, acute phase response, and AAU, has been shown in controlled and uncontrolled studies (123–128). The long-term efficacy and safety of ADA have been demonstrated over 5 years with about half of the patients experiencing sustained remission at any time during the observation period (129). Patients with an inadequate response to the standard dose may benefit from weekly injections of 40 mg of ADA (128). AS patients with advanced disease also show good clinical response to ADA therapy (130,131).

GOL is another humanized monoclonal antibody developed against TNF- α . It is administered SC every 4 weeks. The efficacy of GOL at 50 mg SC every 4 weeks has been shown to be no less effective than GOL at 100 mg SC every 4 weeks (132); therefore, the recommended dose of GOL for AS is 50 mg SC once month. Various RCTs reported that this drug was efficient and safe to suppress the disease activity in patients with active AS (132,133). It was reported that in addition to the fact that this drug suppresses the disease activity, it had positive effects on function, quality of life, and spinal mobility (133). It was reported that both doses were not much different from each other in terms of reducing the axial symptoms. On the other hand, a study that conducted research of efficacy on enthesitis reported that a dose of 100 mg was more significant than a placebo (134).

Several studies have shown that both INF and ADA are efficacious in the treatment of moderate-to-severe Crohn's disease (135–138). In addition, INF and ADA are also effective in inducing and maintaining clinical remission in patients with moderately to severely active ulcerative colitis in whom conventional therapy has failed (139,140). In cases with IBD accompanying AS, INF significantly reduced the exacerbation frequency of IBD when compared to placebos, ETA, and ADA (141). However, IBD exacerbation frequency was similar between patients using ETA and patients using placebos (141).

There are various studies investigating the efficacy of biological drugs in AAU, which is the most frequent nonjoint manifestation in AS. A metaanalysis reported that INF and ETA were significantly more efficient than placebos in preventing AAU attacks (142). Another metaanalysis revealed that ETA was as efficient as SSZ in preventing AAU (143). In an open study, ADA reduced the rate of anterior uveitis flares in patients with active AS (126). However, although ETA has been reported to decrease AAU attacks significantly compared to placebos and to have a similar efficacy to SSZ, a higher number of reported uveitis flares with ETA compared to ADA and INF in two side-effect registries suggest that it may be less effective in preventing uveitis than the monoclonal TNF inhibitors (123,124).

Apart from improving the clinical findings of AS, treatment with TNF inhibitors can reduce spinal inflammation. Double-blind placebo-controlled trials demonstrated that treatment with all four anti-TNF agents currently available in Turkey (INF, ETA, ADA, GOL) resulted in approximately 50% regression of spinal inflammation as assessed by spinal MRI starting at week 12 and this could be maintained up to week 104 (144–147). However, 2 years of treatment with ETA, INF, or ADA did not slow radiographic progression in AS. Radiographs of the spine from patients who received ETA, INF, or ADA were compared with radiographs from TNF-naïve patients in the Outcome in AS International Study (OASIS) database. Radiographic progression as scored by using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) from baseline to the 2-year follow-up did not show any difference between patients treated with anti-TNF agents and patients who had no prior use of those drugs (148–150). Therefore, despite improvement in spinal inflammation, anti-TNF agents could not prevent structural damage in AS patients.

Because of their high cost, TNF- α antagonists should not be continued if adequate response cannot be achieved. Time of evaluation for the efficacy of anti-TNF- α agents should be 6–12 weeks (7). Adequate response is defined as an improvement of at least two units in BASDAI (on a scale of 0–10) by the French Rheumatology Society guidelines (9), whereas it is as a relative reduction of 50% or an absolute change of 20 mm in BASDAI (on a scale of 0–100) according to ASAS recommendations (7).

AS patients who discontinue an anti-TNF- α molecule due to side effects or inefficacy can be switched to another anti-TNF. Among 514 AS patients in a longitudinal observational multicenter study in Norway, 77 patients switched to a second or third TNF inhibitor while 437 patients did not switch. Disease activity and health status 3 months after initiation of treatment were generally better in nonswitchers. However, among switchers,

approximately 40% achieved ASAS20 and 30% achieved ASAS40 response after 3 months of treatment, and there was no clear difference regarding ASAS20 and ASAS40 response among nonswitchers, switchers to a first anti-TNF, and switchers to a second anti-TNF agent (151). An open study, which evaluated the effectiveness and safety of ADA in a large cohort of patients with AS, included 326 patients who had prior use of ETA or INF; of them, 41% achieved BASDAI50 response (126). In an observational study comparing AS patients with RA and psoriatic arthritis, efficacy of TNF switch after failure of one TNF inhibitor was higher in AS than the other two diseases (152). Therefore, switching to another TNF inhibitor appears to be an effective approach in AS, with around one-third of patients showing a good clinical response. On the other hand, there is still no good option for AS patients who cannot take anti-TNF agents due to inefficacy or intolerance. In a 24-week open study, approximately half of the anti-TNF naïve patients treated with rituximab achieved ASAS20 response, and 30% of the patients achieved ASAS partial remission (153). All patients who were regarded as responders at week 24 showed a good clinical response at the end of the first year, with and without a second course of rituximab treatment (154). However, rituximab was ineffective in patients resistant to anti-TNF agents (153). A recent RCT investigated the effect of tocilizumab in anti-TNF naïve AS patients; however, the study had to be terminated due to inefficacy (155). Likewise, in an open study a major response was not observed in AS patients treated with abatacept (156). Secukinumab, which was shown to be effective in reducing clinical or biological signs of active AS in a phase 2 study, may be an alternative to TNF inhibition for both anti-TNF naïve and anti-TNF resistant patients (157).

Messages/recommendations:

- Anti-TNF drugs are effective in treating axial disease, peripheral arthritis, and enthesitis.
- Anti-TNF- α drugs should be preferred in patients who have active disease (BASDAI of ≥ 4) despite conventional treatment.
- Patients with axial disease should have been treated with at least 2 different NSAIDs with maximum tolerated doses for at least 4 weeks, unless there is contraindication to NSAIDs.
- AS patients with peripheral arthritis may be given a therapeutic trial of SSZ.
- Available data do not suggest any additional benefit of using MTX in combination with INF or with any other anti-TNF.
- It seems that anti-TNF drugs are not superior to each other in terms of efficacy. However, the choice of anti-TNF agent should be made according to the current safety data and the patient's characteristics.

Monoclonal antibodies can be preferred in patients with bowel involvement.

- In the absence of response after 12 weeks of treatment with an anti-TNF agent, another TNF inhibitor can be tried.

- Treatment with TNF inhibitors can reduce spinal inflammation detected by MRI. However, anti-TNF agents do not appear to prevent structural damage, at least over 2 years.

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