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Chapter

Treatment Modalities of Ankylosing Spondylitis

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Abstract

Ankylosing spondylitis is a chronic inflammatory arthropathy of young adults which primarily affects the axial skeleton. The pathogenesis of AS is unclear, but it is thought to be caused by an early inflammatory phase followed by ossification that may induce local osteitis. It has also been linked to an increase in morbidity and mortality and is known to have a debilitating impact on QoL of the patients. Whereby, CRP and ESR are used for assessment of the disease activity and determination of treatment efficacy, HLA-B27 is considered the best biomarker for AS diagnosis. The conventional therapeutic regimen like NSAIDs and DMARDs alone are not effective in controlling symptoms and indicators of disease; however, when combined with the physical therapy, great improvement in the QoL of the patients has been observed. The outlook for AS has improved remarkably with the advent of biologics that blocks key inflammatory cytokines such as TNF inhibitors. Biologics aids in halting disease progression, and can be used concomitantly with other medications for pain management. In this chapter, barring surgical interventions, we will discuss about the non-pharmacological and pharmacological therapies routinely employed for the treatment of AS, as well as the novel therapeutics currently under study.

Keywords: ankylosing spondylitis, QoL, HLA-B27, NSAIDs, DMARDs

1. Introduction

Ankylosing spondylitis (AS) is defined as a persistent inflammatory autoimmune disorder, primarily affecting the axial skeleton; mostly joints of the spine, sacroiliac joints (SIJs), and their adjoining soft tissues. Patients with AS usually present with reduced spinal mobility and inflammatory low back pain (LBP). In AS, peripheral joint arthritis corresponds with the disease severity, but it is typically milder when compared to other seronegative spondyloarthropathies (SpA). Radiographic change in the form of sacroiliitis is one of the early sign of AS. In addition, cartilage thinning and bone condensation are also observed on both sides of the SIJs. Progression of this disease can lead to bony ankylosis of both SIJs and joints of the lumbar spine, also known as the "bamboo spine." There are instances where end-stage arthritis develops

in the hip joints resulting in ankylosis, but it is uncommon at other sites. It is common to develop uveitis, and most cases can often be controlled with topical steroids [1–4].

AS is a member of the SpA category of rheumatic disease, i.e., diseases that present common genetic and clinical manifestations. It occurs predominantly in males and presents itself preferably in the early twenties and rarely after 45 years of age. It has been found to occur in 1 of every 200 people. AS is found to be more common in Europe (prevalence estimate of 23.8 per 10,000) followed by Asia (16.7 per 10,000). In India, the estimated diagnosed prevalence of AS is currently 1.65 million, and according to GlobalData's "Pharmaceutical Intelligence Center, " it is anticipated to rise annually by 2.95% from now until 2028 to reach 2.0 million [5–8]. The etiology of AS remains ambiguous to date, likewise other autoimmune disorders, AS is known to develop through a complex interplay of genetic and environmental factors. Studies have reported more than 100 gene loci to be in association with AS, but in sync, they account for only about 30% of AS heritability. A strong correlation of major histocompatibility antigen (MHC) class I allele HLA-B27 with AS has been established, thus HLA-B27 remains the best-known biomarker for the prognosis of AS, although only 1–2% population with HLA-B27 positive allele are known to develop AS. In addition, elevated levels of CRP and ESR are also detected in the serum of patients with AS [2, 4].

Treatment of patients with active AS involves improving functional ability, maintaining spinal flexibility, correct posture, and relieving symptoms. The conventional therapeutic regimen like Disease Modifying Anti Rheumatic Drugs (DMARDs) and Non Steroidal Anti Inflammatory Drugs (NSAIDs) are not really effective in controlling symptoms and indicators of disease, as well as in halting disease progression. However, with the advent of biologics that blocks key inflammatory cytokines such as Tumor Necrosis Factor (TNF), the outlook for AS has improved. In the short and medium-term, ongoing research has shown that these agents are effective and safe. Longer-term studies are also needed to determine whether these medicines are true disease modifiers in AS. In this chapter, we will discuss in-depth the treatment modalities currently employed and understudied for the treatment of AS [2, 4, 9].

2. Non-pharmacological treatment

There are numerous pharmacological and non-pharmacological treatments available to alleviate back and SIJ stiffness and pain while enhancing spinal and peripheral joint mobility. But, the long-term management of AS calls for a mix of medication, physical therapy, and psychosocial interventions. The main challenge is therefore to reduce the impact of AS on patients and the healthcare system. A key component of managing AS is supervised physical therapy, which has the potential to increase the efficacy of exercise regimens and result in a quicker and longer-lasting improvement in AS symptomatology [10].

2.1 Physical therapy

Physical therapy is listed as one of the non-pharmacological therapeutic strategy for the treatment of AS in contemporary, internationally accepted expert consensus documents because AS is an evolving condition. Physical therapy may include posture training, strengthening, flexibility or stretching and deep breathing exercises, which can be provided both individually and in groups. Even though many people with AS can benefit from exercise, not all programs are effective for everyone. Some people

might benefit from gentle, low-impact exercises or those that concentrate on easing pain or stress [11, 12].

2.1.1 Strengthening, stretching and deep breathing exercises

The Spondylitis Association of America claims that developing stronger core muscles can help people with AS reduce back pain as well as pressure on their spines. The muscles that support the spine is known as core muscles, including the abdominal muscles. Stretching exercises such as spinal flexion can help the patient with AS in maintaining their mobility and reducing the risk of developing joint fusion. AS patients may experience breathing problems due to limited chest expansion. Therefore, physiotherapists may advise deep breathing exercises that aid in strengthening the diaphragm and increasing lung capacity [11].

2.1.2 Balneotherapy

Balneotherapy is a traditional physical therapy that involves spa treatment. Since ancient times, it has been used to treat rheumatic diseases. One physiological result of being exposed to heat during a spa treatment is increased blood circulation in the tissues. Heat exposure to inflamed tissues promotes the flow of fresh blood through the tissues and speeds up the removal of toxic elements, thereby promoting tissue healing [13].

2.1.3 Chiropractic therapy

The term "chiropractic" is used to describe a wide range of therapeutic modalities. These may combine manual therapies, passive modalities, exercise regimens, high-velocity spinal manipulation, no touch therapy, touch therapy, and pain education, but are not limited to those. The American College of Rheumatology, the Spondylitis Association of America, and Spartan published the "Treatment Guidelines in Axial Spondyloarthritis" in 2015, and they strongly advise against using high-velocity thrusts to manipulate the spine in AS patients who have spinal osteoporosis or spinal fusion. Axial spondyloarthritis patients should not undergo spinal manipulation due to the risk of undiagnosed osteoporosis and the potential side effects of manipulating joints that are actively inflamed. Prior to starting chiropractic treatment, extreme caution should be exercised [14].

Due to the risk of undiagnosed osteoporosis and the unknown effects of joint manipulation in actively inflamed joints, spinal manipulation in any patient with established axial spondyloarthritis should be avoided. Prior to starting chiropractic treatment, extreme caution should be taken. Spinal fractures, spinal cord damage, and even paraplegia are risks for people with axial spondyloarthritis [14].

2.2 Yoga

Yoga is a discipline involving mind–body practices. In both clinical and non-clinical populations, it promotes health benefits through physical postures, breathing techniques, relaxation techniques, and meditation. Yoga is known to improve various musculoskeletal problems such as back and neck pain, osteoarthritis, etc. Additionally, it has been effective in improving pain management and spinal flexibility in chronic low back pain patients. Researchers found that yoga practice can help

reduce inflammation and improve the range of motion in musculoskeletal disorders by down-regulating the nuclear factor κ β (F-κβ) [15].

In a study, researchers validated a yoga module for the treatment of AS based on the improvements observed in the spinal flexibility and chronic pain. The module included amalgamation of different yoga practices such as loosening, breathing, asanas, pranayama and yogic cleansing techniques. It was concluded that following the module for at least 30 minutes every day for a minimum of 3 days a week for 3 months, can help AS patients in improving their quality of life (QoL). Moreover, the use of breathing exercises and relaxation techniques can potentially increase one's pain tolerance and sensitivity. Increased endorphin levels and decreased hypothalamus–pituitary–adrenal (HPA) axis activity are also found to be linked to yoga practice [16].

3. Pharmacological treatment

3.1 NSAIDs

NSAIDs are a broad class of medications with a wide range of structural and functional characteristics. Most of these are weak organic acids (comprising of an acidic moiety along with an aromatic functional group). NSAIDs can be broadly classified based on their chemical structure, Cyclooxygenase (COX)/prostaglandin-endoperoxide synthase (PGHS) inhibition, and bioavailability in the serum. NSAIDs primarily function by inhibiting the COX enzyme (COX-1 and COX-2), which converts arachidonic to prostaglandins (PGs), thereby mediating inflammation and pain. COX-1 exclusively produces PGs crucial for maintenance normal physiological functions (maintenance of endocrine and renal functions, integrity of gastric mucosa, and hemostasis). Under normal physiological conditions, COX-1 is found in higher concentrations in the platelets, vascular endothelial cells, the stomach, and kidney collecting tubules. On the contrary, COX-2 exclusively produces PGs that mediates local inflammation, and is almost undetectable in most of the tissues. Traditional NSAIDs are non-selective meaning they can inhibit both COX-1 and COX-2. The new class of NSAIDS that selectively inhibits COX-2 is known as COX inhibitors [17].

NSAIDs form the first line of treatment for patients with active AS because of their efficacy in reducing pain and inflammation. Phenylbutazone was the first most popular drug to be used for AS treatment, giving good results. However, drug tolerance to patients was poor, additionally causing hematological adverse events (severe agranulocytosis). Several clinical trials conducted to ascertain the effectiveness and safety of NSAIDs in subjects with active and stable AS were evaluated. Results from 9 out of 15 clinical trials showed that indomethacin, a COX inhibitor was associated with neurological adverse events (AEs) such as headache and dizziness. Moreover, indomethacin 50 mg slow release tablets were found to be equally effective to indomethacin 25 mg capsule, but the former had fewer side effects. In most of the subjects, piroxicam (traditional NSAID) and aceclofenac (COX inhibitor) were found to be better tolerated than indomethacin. Aceclofenac exhibits lower risk of developing cardiovascular, renal, and gastrointestinal side effects when compared to traditional NSAIDs, naproxen and diclofenac [18–20].

There are no preferred NSAIDs for treatment of AS, but it is conditionally recommended that NSAIDs can be used continuously in subjects with persistently active, symptomatic diseases, with doses adjusted according to the severity of the disease, patient preferences, and co-morbidities. Since, the side effects outweigh the benefit

of continuous treatment with NSAIDs in delaying the radiographic progression of the disease. On-demand treatment is conditionally recommended for management of subjects with stable disease activity [20].

3.2 Analgesics, muscle relaxants and corticosteroids

In patients with poor tolerance to NSAIDs, adjuvant therapy can be given which includes analgesics, muscle relaxants, and corticosteroids. In patients with NSAID intolerance, analgesics such as paracetamol (acetaminophen) and dextropropoxyphene is given concomitantly with muscle relaxant like tetrazepam in order to reduce pain and stiffness. Not much data is available on the use of glucocorticoids for the management of AS. However use of low and moderate-dose corticosteroids orally, has not been found much effective in relieving AS symptoms. In recent RCTs (randomized controlled trials), pulse therapy using a high dose of corticosteroids both orally and intravenously has produced favorable results. It is advised that administration of corticosteroid injections should generally be restricted to no more than three times per year, with at least 3 months passing between each injection in the same joint [19–23].

3.3 DMARDs

DMARDs form the second line of treatment for patients with AS who do not show promising results with NSAIDs and analgesics. They are pharmaceutical agents that suppress autoimmune activity and slow down or stop joint degeneration in order to promote remission. Given that DMARDs are slow-acting medications with a delayed onset of between 6 weeks and 6 months, the treatment should be started as soon as possible because early implementation yields better outcomes [24].

There are different types of DMARDs such as Biologic DMARDs (bDMARDs), targeted synthetic DMARDs (tsDMARDs), and traditional synthetic DMARDs (csD-MARDs). For patients with newly diagnosed rheumatoid arthritis (RA), csDMARDs are typically used as the first line of treatment. If first-line therapy is not tolerated or is ineffective, bDMARDs or tsDMARDs are advised [24].

csDMARDs such as Leflunomide (LEF), methotrexate (MTX), sulfasalazine (SSZ), and hydroxychloroquine (HCQ) are used more frequently than other agents with a lower efficacy and safety profile, which includes gold salts, azathioprine, d-penicillamine, cyclosporine, minocycline, etc. The mechanism of action of these medications results in a non-targeted immune system suppression [24].

3.3.1 Methotrexate

As an anti-metabolite, MTX inhibits dihydrofolate reductase (DHFR) through competitive inhibition, thereby preventing DNA synthesis. MTX has exhibited promising results in the treatment of RA, but in AS not much evidence is available on the efficacy of the drug. MTX is rarely used for AS treatment but is prescribed to AS patients who show intolerance to SZZ [25].

3.3.2 Sulfasalazine

Following its initial development and use in RA, SSZ showed promise in the treatment of inflammatory bowel disease. Salicylic acid and the antibacterial compound sulfapyridine are combined to form SSZ. SSZ is normally prescribed in the dosage

of 500 or 1000 mg twice a day. The rationale for using SSZ in AS stems from the description of inflammatory lesions in the ileum of AS patients, as well as the frequent correlation between AS and inflammatory bowel disease (IBD). In addition, it has been proposed that intestinal bacteria may cause AS (such as *Klebsiella pneumoniae*). As a result, SSZ has been investigated as a potential therapeutic option for AS patients [19].

In another study conducted, SSZ did not prove to be effective in the management of AS in terms of reducing pain, disease activity, radiographic progression, or enhancing physical function and spinal mobility. Contrary, SSZ has exhibited statistically significant benefits in lowering the ESR and reducing spinal stiffness. The effect size, however, was extremely small and not clinically significant. Moreover, it was observed that withdrawal due to side effects was more common in patients with AS treated with SSZ [26].

SSZ or MTX are conditionally recommended in patients who have prominent peripheral manifestations (such as peripheral arthritis) with few or no axial skeleton symptoms or when TNFi are not available or patients exhibiting contraindications to TNFi. In patients with contraindications to TNFi due to tuberculosis, other chronic infections, or high risk of recurrent infections, SSZ is preferred over secukinumab, ixekizumab and tofacitinib [20].

3.4 Bisphosphonates

Bisphosphonates are stable chemical derivatives of naturally occurring inorganic pyrophosphates (PPi). The PPi is formed by the esterification of two phosphate groups. Bisphosphonates act by promoting apoptosis of osteoclasts, thus they have become the primary therapy for the treatment of skeletal conditions marked by increased osteoclast-mediated bone resorption [27]. Among the conditions commonly treated with bisphosphonates are Paget's disease, hypercalcemia, osteoporosis and malignant bone diseases. Furthermore, bisphosphonates have anti-inflammatory properties, which may explain their use in treating inflammatory rheumatic diseases like AS [28].

Studies have reported positive results in the treatment of AS with pamidronate, as it successfully treated both spinal and peripheral disease, enthesitis included, when applied intravenously. Clinical improvements, in general, were found to be mild and delayed, but they did not correlate with the laboratory parameters of inflammation. Alternatively, pamidronate favored bone turnover by reducing markers of bone resorption and formation. Another study involving a comparison of infliximab, it was exhibited that short-term therapy for AS with neridronate is effective. Thus, for long-term treatment of AS, bisphosphonates alone or in combination with anti-TNF may be considered. It was observed that turnover of subchondral bone is reduced by bisphosphonates, which also have anti-inflammatory effects turnover [28–30].

3.5 Thalidomides

An analogue of racemic glutamic acid, thalidomide is composed of the S(−) and R(+) enantiomers, which interconvert under physiological circumstances. The R(+) form appears to act as a sedative, likely via sleep receptors in the forebrain, whereas the S(−) form potently inhibits the release of tumor necrosis factor (TNF) from peripheral mononuclear blood cells [30]. Since the 1990s, thalidomide has been used to treat AS in China, where it has been proven to be both effective and safe over the long term. Strict adherence to the System for Thalidomide Education and Prescription Safety (STEPS) programme is undertaken while prescribing this medication, because

of the drug's toxicity to the developing fetus. Thereby explaining why the thalidomide rates are significantly lower in patients with shorter disease duration [31, 32].

3.6 Cytokine therapy

3.6.1 Tumor necrosis factor inhibitors

The development of TNF inhibitors (TNFi) has been the most significant advancement in the management of AS in recent years. These are referred to as biologics chiefly targeting the inflammatory modulators that are known to play important role in disease pathogenesis. TNFi in the treatment of AS mainly focuses on TNF-alpha (TNF-α) inhibition. TNF-α is known to play a central role in the inflammation of the axial skeleton and entheses in AS patients. It can activate various signaling pathways, thereby mediating the release of various inflammatory mediators like interleukins (ILs), and the activation of immune cells such as T cells, B-cells, or macrophages. TNFi is given to patients who exhibit intolerance to NSAIDs and analgesics and administered subcutaneously with infliximab as an exception, which is given through infusion [32–36]. A systematic review demonstrated that after etanercept [(1.2% of the patients producing anti-drug antibodies (ADAs)], golimumab was the least immunogenic (3.8%) of the TNFi, followed by infliximab (25.3%), adalimumab (14.1%), and certolizumab (6.9%) [37].

TNFi is strongly recommended to patients with active disease exhibiting no response or contraindications to at least two different NSAIDs therapy for over a month. There is no preferred choice of TNFi for the treatment of AS. In case of patients showing secondary non-response to the first TNFi used for treatment, switching to another TNFi is conditionally recommended. In patients with recurring uveitis or inflammatory bowel disease (IBD) use of monoclonal TNFi is recommended. Patients with stable disease activity being treated with combination of NSAID and TNFi, discontinuation of NSAID and treatment of TNFi alone is recommended [20].

3.6.1.1 Etanercept

Etanercept (ETN) is a TNF-α binding and TNF-α inactivating dimeric fusion protein composed of the human p75 TNF receptor and the Fc region of human Immunoglobulin G1 (IgG1). Unlike adalimumab (ADA) and IFX, it also binds to lymphotoxin-α [33]. ETN neutralizes this fusion protein, which is highly compatible with soluble TNF-α in plasma and on the surface of cell membranes, resulting in loss of the biological activity of TNF-α and inhibiting atypical immune response and release of cytokines mediated by the receptor, effectively treating AS [38].

3.6.1.2 Infliximab

Infliximab (IFX) is used to treat some diseases by boosting the immune system of the body. It is a purified, chimeric IgG monoclonal antibody protein derived from recombinant DNA that inhibits TNF-a in both murine and human components. A signaling protein called TNF-α plays a role in systemic inflammation and acute phase reactions. Neutrophils, mast cells, eosinophils, CD4+ lymphocytes, NK cells, macrophages, and neurons all produce it. By inhibiting TNF-α, the inflammatory response cascade is stopped, which improves the state of the disease (Crohn's disease, psoriasis, etc.). IFX is known to have 7–12 days of half-life in adults [39, 40]. IFX is prescribed

as 5 mg/kg IV at 0, 2 and 6 weeks to AS patients. Different studies that were done to evaluate the safety and efficacy of IFX exhibited positive results. Most of the patients with the active disease when given prescribed doses of IFX showed decreased morning stiffness and acute phase reactants. Significant improvement in the QoL and bath indices (disease activity and functional ability) of the patients was observed. In addition, IFX decelerated the structural progression of the disease in AS patients [41].

Long-term treatment of AS patients with ETN has shown a reduction in the radiographic progression of the disease. Similar to IFX, treatment with ETN ensured lower levels of acute-phase reactants and improved bath indices, spinal mobility, and QoL, when compared with baseline. No adverse events (AE) or Serious AE (SAE) was observed in the patients [41].

3.6.1.3 Adalimumab

ADA is the first fully humanized recombinant IgG1 monoclonal antibody (mAb) that inhibits TNF-α to exert its effects, thereby reducing the potential for immunogenicity, in contrast to IFX, which is a chimeric antibody made up of both mouse and human domains that may trigger immune reactions that could limit its long-term use in patients with chronic conditions like rheumatoid arthritis. ADA has a very high affinity for TNF and is effective in neutralizing TNF in bioassays. The kinetic binding parameters of ADA and IFX are quite similar. Contrary ETN dissociates from TNF much more quickly [42]. ADA works by neutralizing the bioactivity of TNF-α. This is done by preventing the interaction of TNF-α with the cell surface TNF receptors. ADA is given subcutaneously in dosage of 40 mg every alternate week [43].

ADA demonstrated long-term efficacy and safety in patients with AS. ADA has exhibited greater tolerance in patients. It greatly improved the CRP levels, physical function, disease activity, and low back pain (LBP) in patients. When administered every other week, most of the patients achieved Assessment in AS response criteria (ASAS20) by week 12, and 50% of the patients achieved ASAS40 by week 52. Additionally, ADA therapy resulted in a notable reduction of acute inflammatory lesions [41].

3.6.1.4 Golimumab

Golimumab was developed by introducing human Ig genes into transgenic mice, which were then engineered to express human IgGs. Golimumab's heavy and light variable chain regions are made of an amino acid sequence that is remarkably similar to that of the human sequence (heavy chain sequence, 98%; light chain sequence, 100%). The bivalent Fab region is particular to human TNF. TNF is, therefore, less likely to circulate and bind to receptors as a result. The Fc regions' amino acid sequence matches IFX's exactly [44].

About 29 patients with active AS, a BASDAI score > 4, and a back pain score > 4 was randomized in the GO-RAISE study in a 1.8:1.8:1 ratio to receive subcutaneous injections of golimumab (50 or 100 mg) or a placebo every 4 weeks. Compared to patients in the placebo group, a significant number of patients receiving golimumab experienced an ASAS20 response (p.001) [44, 45].

Another study compared the impact of golimumab and pamidronate on MRI inflammation and clinical efficacy in AS. In a 2:1 ratio, patients who met the criteria were randomized to receive either golimumab (50 mg subcutaneously) or pamidronate (60 mg intravenously) every 4 weeks for 48 weeks. The patients also had to meet the ASAS criteria for AS and active disease (BASDAI score 4). There were recruited

30 patients. Inflammation of the spine and sacroiliac joints, as well as inflammatory markers (ESR and CRP), BASDAI, BASFI, and the Ankylosing Spondylitis Disease Activity Score (ASDAS), were significantly reduced by golimumab. Pamidronate was linked to improvements in patient-reported outcomes (PRO), and response rates to ASAS20 and ASAS40 were comparable [44–46].

3.6.1.5 Certolizumab

Certolizumab (CZP), commonly referred to as CZP pegol is a humanized antigen-binding fragment (Fab') conjugated to polyethylene glycol (PEG). It is distinct from other TNF-inhibitors because it lacks an Fc region, which reduces the possibility of Fc-mediated effects like complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC). CZP does not induce CDC and ADCC, as shown by in vitro studies of ADA, IFX, and ETN. Additionally, in vitro research has shown that CZP inhibits lipopolysaccharide-induced cytokine production more effectively than other TNF-inhibitors, particularly ETN, and does not trigger apoptosis in activated peripheral blood lymphocytes [47].

The ASAS20 response rate at week 12 was significantly higher for the CZP 200 and 400 mg arms compared to placebo (57.7 and 63.6 vs. 38.3). A significant difference was observed at week 24 between the combined CZP arm and placebo in BASDAI (−3.05 vs. −1.05), BASFI (−2.28 vs. −0.40), and BASMI (−0.52 vs. −0.07). As early as week 1, improvements were noticed. Remarkable improvement was observed in AS subpopulation with CZP compared to placebo. Adverse events (AEs) and serious AEs were reported in 70.4 and 4.7% patients respectively in the CZP arm. No fatalities or cancers were reported [47, 48].

3.6.2 Interleukin inhibitors

Interleukins (ILs) play a significant role in the pathogenesis of AS. IL-17 has emerged to play a role in AS patients as an inflammatory mediator. Moreover, elevated serum levels of IL-17 and circulating Th17 cells have been reported in AS patients. Furthermore, endogenous interactions between IL-17A and RANKL stimulate osteoclastic activity in bone, resulting in osteoporosis, bone erosions, and osteopenia in AS patients [43, 49].

Treatment with IL-17 inhibitors (secukinumab and ixekizumab) is recommended in patients with active disease who show contraindications to TNFi. In primary non-responders to TNFi, use of IL-17 inhibitors is conditionally recommended. In patients with IBD use of IL inhibitors is not recommended. Contraindications to TNFi due to congestive heart failure or demyelinating disease, IL-17 inhibitors are preferred [20].

3.6.2.1 Secukinumab

Secukinumab is a recombinant humanized mAb that targets Interleukin-17 (IL-17), which is a proinflammatory cytokine involved in various pathological processes. Its efficacy in the management of AS has been demonstrated by many clinical trials in 2016. In addition, secukinumab has an exemplary safety profile. Secukinumab targets IL-17A specifically, thus inhibiting its binding with IL-17 receptor and cytokines expression. Therefore, normalizing the inflammation and combating pathogenic gene expression, epidermal hyper-proliferation, and T-cell infiltration. Patients with active AS who have exhibited an inadequate response to NSAIDs and TNFi therapy

may benefit from secukinumab, according to the UK's National Institute for Health and Care Excellence (NICE). Secukinumab is administered under the skin, and the recommended dosage is 150 mg [50, 51].

3.6.2.2 Ixekizumab

Ixekizumab (IXE) is an IgG4 mAb, that binds to IL-17A (both IL-17A and IL-17A/F) with high specificity and affinity. IXE specifically binds to the IL-17A cytokine to block interaction with the IL17 receptor, preventing target cells from releasing proinflammatory cytokines and chemokines that have an impact on cellular components later on. IXE does not bind to the human Fc I, IIa, or IIIa receptors or to the complement subunit C1q, according to in-vitro binding tests [49].

IXE has been shown to be both safe and effective in phase II trials. In comparison to placebo-treated AS subjects, IXE-treated AS subjects had a 73% response rate for the European league against rheumatism (EULAR). Moreover, it was effective for patients who had previously failed to respond to one or more TNF inhibitors. IXE is administered subcutaneously and the recommended dosage is 160 mg every alternate week for 12 weeks, after that it can be given at a dose of 80 mg for 4 weeks [49].

3.6.3 Janus kinase inhibitors

Inflammatory and autoimmune diseases are influenced by the expression of molecules such as survival factors, chemokines, cytokines, and other molecules that promote leucocyte cell proliferation and trafficking. Since the JAK family has attracted significant interest for the potential treatment of inflammatory diseases, a variety of JAKi have been created, each with a unique selectivity profile against JAK1, JAK2, JAK3, and non-receptor tyrosine-protein kinase 2 (TYK2). The aberrant immune response is triggered by cytokines whose signal transduction is disrupted in AS [52, 53].

3.6.3.1 Tofacitinib

Tofacitinib is an orally available first-in-class pan-JAKi, which potently inhibits JAK3 and JAK1 while only weakly inhibiting JAK2 [53]. It has long been used concomitantly with MTX for the treatment of RA [54].

In a phase II trial, tofacitinib 10 mg twice daily ASAS20 response rate was predicted by the Emax model analysis of the primary endpoint to be 67.4%, 27.3% higher than the actual response rate. Tofacitinib 5 mg twice daily Assessment of Spondyloarthritis International Society 20 (ASAS 20) response rate was significantly higher than placebo (80.8 vs. 41.2%), and tofacitinib 2 and 10 mg twice daily also showed a higher response rate than placebo (51.9 and 55.8%, respectively; not significant). Secondary endpoints typically showed tofacitinib 5 and 10 mg twice daily to be more effective than placebo. The dose–response relationship was evident in objective endpoints (including MRI). There were no unexpected safety findings and adverse events were comparable between treatment groups. By week 16, dose-dependent laboratory outcome changes had nearly reached baseline [55].

Another phase III trial (NCT03502616) found that tofacitinib significantly increased the ASAS 20 response rate (56.4%) compared to placebo (29.4%) and the

ASAS 40 response rate (40.6%) compared to placebo (12.5%). Up to week 16, AEs occurred in 54.9% and 51.5% patients receiving tofacitinib and placebo, respectively. Whereby, 1.5 and 0.7% patients receiving tofacitinib and placebo respectively experienced serious AEs. When compared to a placebo, tofacitinib significantly outperformed it in treating adults with active AS. No brand-new dangers to safety were found [56].

In patients with coexisting ulcerative colitis, use of tofacitinib (approved for the treatment of ulcerative colitis) is preferred over IL-17 inhibitors if treatment with TNFi is not an option. In patients with peripheral manifestations, tofacitinib is conditionally recommended if contraindications to SSZ or MTX are exhibited [20].

3.6.3.2 Upadacitinib

It is a second-generation JAKi inhibitor that targets the JAK1 enzyme primarily. Upadacitinib works by inhibiting the Janus kinases (JAK), a family of four tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) that play a role in the development of immune-mediated inflammatory diseases (IMIDs). The JAK–STAT pathway's ability to transduce growth factor- and cytokine-mediated signals intracellularly is further hampered by JAK inhibition. JAKs control gene expression, hematopoiesis, and immune cell function by phosphorylating signal transducers and activators of transcription (STATs). Upadacitinib stops STATs from becoming phosphorylated and from becoming activated inside of cells, which lessens their pro-inflammatory effects. Compared to JAK2, JAK3, and TYK2 subtypes, upadacitinib inhibits JAK1 more potently and selectively [57].

Upadacitinib 15 mg (93 patients) or a placebo (94 patients) were given to 187 patients at random. Of these, 178 (95%) patients (89 in the upadacitinib group and 89 in the placebo group) finished period 1 on the study drug. At week 14, significantly more patients in the upadacitinib group than in the placebo group had an ASAS 40 response (48%). In the upadacitinib group, 58 (62%) of 93 patients reported adverse events, compared to 52 (55%) of 94 patients in the placebo group. Creatine phosphokinase elevation was the most typical side effect in the upadacitinib group (9% of patients) (**Table 1**) [57, 59].

Cytokine therapy	Medication	FDA approval granted for treatment of AS
TNF inhibitors	Etanercept	July 2003
	Infliximab	December 2004
	Adalimumab	July 2006
	Golimumab	April 2009
	Certolizumab	October 2013
IL inhibitors	Secukinumab	January 2016
	Ixekizumab	August 2019
JAK inhibitors	Tofacitinib	December 2021
	Upadacitinib	April 2022

Table 1.
List of biologics approved by US FDA for treatment of patients with active AS [58].

4. Therapies and drug targets currently under study

4.1 Ustekinumab

The polymorphism of IL23R gene that encodes IL-23 receptor has exhibited strong association with AS, suggesting its involvement in the disease pathogenesis. Contrary to osteoarthritis patients without spinal disease, patients with active AS demonstrated higher number of IL-12, and IL-23 positive cells bone marrow of facet joints [43].

Ustekinumab is a humanized IgG1κ mAb that binds to p40-subunit commonly shared by IL-12 and IL23. It is used in the treatment of psoriatic arthritis, significantly inhibiting the radiographic progression. Since ustekinumab is well tolerated in patients, it has emerged as a novel biologic to be evaluated for the treatment of AS. In a prospective, open-label, single-arm, proof-of-concept study [treatment of patients with active AS (TOPAS)], 65% of the subjects who were administered ustekinumab achieved the primary endpoint–ASAS 40 response at week 24. Furthermore, secondary endpoints revealed clinically significant results. About 75% of the subjects achieved ASAS 20 response; in addition to 55% subjects who achieved BASDAI 50 response [53, 60].

4.2 Stem cell therapy

The first characterization of mesenchymal stem cells (MSCs) was formed in 1976. They are multipotent, meaning they have the ability to self-renew, and to differentiate into different cell types, such as adipocytes, osteoblasts, and chondrocytes. Bone marrow, umbilical cord, adipose tissue, amniotic fluid, molar cells, and peripheral blood are all sources of MSCs [61].

The efficacy and safety of MSC therapy have been demonstrated in a variety of studies, as well as in the treatment of autoimmune diseases, SLE, and MS. There are numerous clinical trials currently underway about MSC transplantation in disorders related to it, including a phase I/II clinical trial to evaluate the safety and clinical outcomes of MSC transplantation in AS patients. MSCs play important roles in immune regulation, making their transplantation a viable therapeutic option for AS patients who cannot tolerate inflammatory drug therapy. Previous studies have demonstrated that AS patients have low Treg cell counts, low B cell counts, and abnormal B cell function, with the ensuing auto-antibodies playing a role in the pathogenesis of AS [61].

5. Conclusion

NSAIDs are the first-line of treatment for patients with AS. Whereby, SSZ or other DMARDs forms the second-line treatment, and are recommended conditionally in limited clinical circumstances. In patients with no response to NSAIDs, TNF inhibitors are preferred, which tends to halt the disease progression by inhibiting the activity of TNF-α. IL inhibitors like secukinumab or ixekizumab is recommended for patients with active disease who have heart failure or demyelinating disease as a contraindication to TNF inhibitors, and in primary non-responders to TNF inhibitors. Contrary, IL inhibitors are not recommended in patients with IBD or recurrent uveitis, as TNF inhibitors are better options. Tofacitinib (JAKi) is a potential second-line option for patients with contraindications to TNF inhibitors other than infections [22]. Medications alone cannot suffice for the long term management of AS.
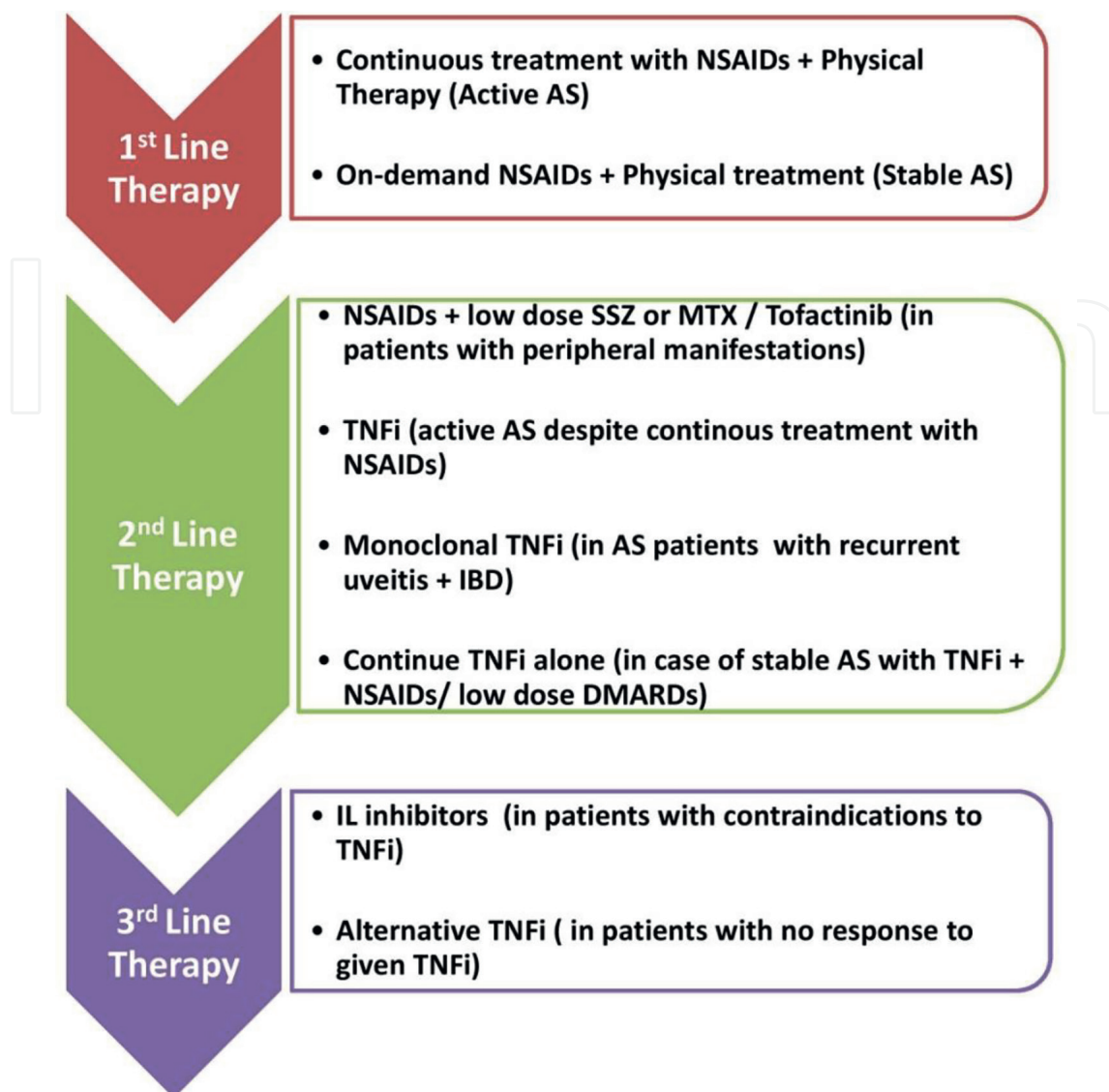
Figure 1.
Recommendations for treatment of AS given by American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network [20].

Therefore, physical therapy or yoga should be advised to the patients as it helps with improvement of AS symptoms (**Figure 1**).

Conflict of interest

The authors declare no conflict of interest.

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