Review Article

Ankylosing Spondylitis: A Comprehensive Review of Clinical Manifestations, Imaging Modalities, Pharmacological Management, and Surgical Interventions

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Abstract

Ankylosing spondylitis (AS) is a long-lasting advancing autoimmune inflammatory condition that mainly targets the axial skeleton, sacroiliac joints and enthuses. It frequently results in pain stiffness and structural damage including syndesmophyte formation and spinal ankylosis. AS has a robust genetic foundation particularly linked to the HLA-B27 gene. It also encompasses intricate interactions among immune dysregulation, microbial triggers and environmental influences. Extra-articular manifestations including anterior uveitis gastrointestinal involvement and cardiac abnormalities, add to the disease burden. Diagnosis is based on clinical assessment imaging techniques such as X-ray and MRI along with corroborative lab tests. Strategies for treatment comprise NSAIDs biologic DMARDs (notably TNF-α inhibitors) IL-17 inhibitors and new JAK inhibitors as well as physical therapy and changes in lifestyle.Severe deformities or complications are the only cases in which surgery is performed. This article examines the etiology and clinical features of ASas well as diagnostic methods and evidence based treatment recommendations. It emphasizes that early diagnosis and targeted therapy are essential for improving patient outcomes.

Keywords: Ankylosing Spondylitis, Axial Skeleton, HLA-B27, NSAIDs, Inflammation.

Introduction

Ankylosing spondylitis is a long-lasting inflammatory rheumatic disease that mainly impacts the axial skeleton. The defining characteristic of this condition is sacroiliitis which is accompanied by enthesitic inflammation (the sites where tendon, ligament, or capsule attaches to bone) and syndesmophyte development resulting in spinal ankylosis in the later phases [1]. Estimates of prevalence differ across populations ranging from 0.1% to 2%. The male-to-female ratio is approximately 5:1 with the peak age of onset occurring between 15 and 35 years [2]. The most frequent extra-articular manifestation of seronegative spondyloarthropathies is ocular involvement particularly as anterior uveitisOf the seronegative spondyloarthropathies AS is recognized for having the strongest link to anterior uveitis [3]. This part will concentrate on the eye-related manifestations of AS.Ankylosing spondylitis (AS) is a type of arthritis that primarily targets the spine, sacroiliac joints, spinal attachment sites and other axial bones leading to chronic inflammation and impairment of joint function.AS is a long-lasting inflammatory autoimmune condition that manifests clinically as intense pain, restricted movement, and spinal mobility issues along with effects on organs outside the skeletal system [4].AS often affects young adults and is more prevalent in men, with HLA-B27 positivity being substantially linked to more frequent attacks [5]. The estimates of incidence and prevalence range from 0.05 to 1.4 per 10,000 individuals annually and from 0.1% to 1.4%, respectively [6]. NSAIDs, methotrexate, azathioprine, and biosynthetic disease modifying anti-rheumatic drugs (BDMARDs) are now effective treatments for systemic AS symptoms [7]. AS significantly impacts patients physical and mental well-being leading to substantial social costs however early diagnosis and proactive treatment can delay and reduce the occurrence of issues while also contributing to a better AS prognosis. AS belongs to a category of conditions referred to as seronegative spinal arthritis (SpA) which have no known cause. Epidemiological data that are currently available demonstrate that inflammation is a significant factor in the etiology of AS mainly via the interplay of genetic and environmental factors that foster inflammation [8]. There have been associations with elevated risk for MHC-encoded class I alleles HLA-B27 endoplasmic reticulum aminopeptidase (ERAP1) and IL-23R. The immune system consists of various immune cells cytokines and markers that regulate the immune response and inflammation. SpA is currently characterized as a polygenic autoinflammatory disease where abnormalities in the innate immune system can have a significant impact marked by the abnormal activation of both innate and innate like immune cells. With the advancement of high-throughput sequencing technology our understanding of the immune system's function and key cell types in AS pathogenesis is expanding. Nevertheless effective treatments have not yet been created, and numerous patients encounter issues or become or deemed unsuitable for current pharmacological treatments [9].

Important point to consider for AS

- Several mechanisms related to HLA-B27 are being studied the arthritogenic hypothesis the unfolded protein response hypothesis and the free heavy chain hypothesis.[10]
- Die bisheridentifiziertennichtHLA-B27-Gene könnteneine Rollebei der Verarbeitung von HLA-B27-Molekülen oderbei der Regulation von Zytokinenspielen [11].

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- Beyond inflammation, patient disability in AS is caused by bone erosion and the formation of syndesmophytes however these processes seem to be independent of inflammation.
- A key future focus is to comprehend the mechanisms behind bone erosion and syndesmophyte formation in AS as well as how these mechanisms can be managed [12].

History and Origin Of AS

The following conditions are classified as sero negative spondyloarthropathies:

- AS (Ankylosing Spondylitis)
- Reactive arthritis (known as Reiters syndrome as well)
- Psoriatic arthropathy
- Spondylitis linked to nonspecific inflammatory bowel diseases (IBD) including Crohn's disease and ulcerative colitis.
- Undifferentiated spondyloarthropathies [13].
- In1970 doctors characterized the common clinical symptoms of seronegative spondyloarthropathies as a separate category of diseases from rheumatoid arthritis.

Patients with AS (Bechterew disease MarieStrumpell disease) are deemed seronegative as they usually exhibit a negative rheumatoid factor and antinuclear antibody [14]. Spondyloarthropathy encompasses a collection of rheumatologic diseases that share similar clinical characteristics:

1. Inflammation of joints (mainly in the axial spine and sacroiliac regions although peripheral joints can also be involved) [15].
2. Enthesitis characterized by inflammation at the sites where tendons, ligaments, and joint capsules attach to the bone [16].
3. Extra-articular manifestations including uveitis gastrointestinal (GI) disorders mucocutaneous lesions and cardiac abnormalities [17].
4. The existence of the Human Leukocyte Antigen (HLA)-B27 gene [18].

1. ETIOLOGY Of AS

AS being an autoimmune disease arises from intricate interactions between genetic predispositions and environmental influences. Even though the last few decades have seen considerable advances the cause of AS is still not fully understood [19]. So far research has uncovered certain elements that could be linked to the manifestation of AS such as genetic predisposition, immune response, microbial infection, and hormonal irregularitie [20,22].

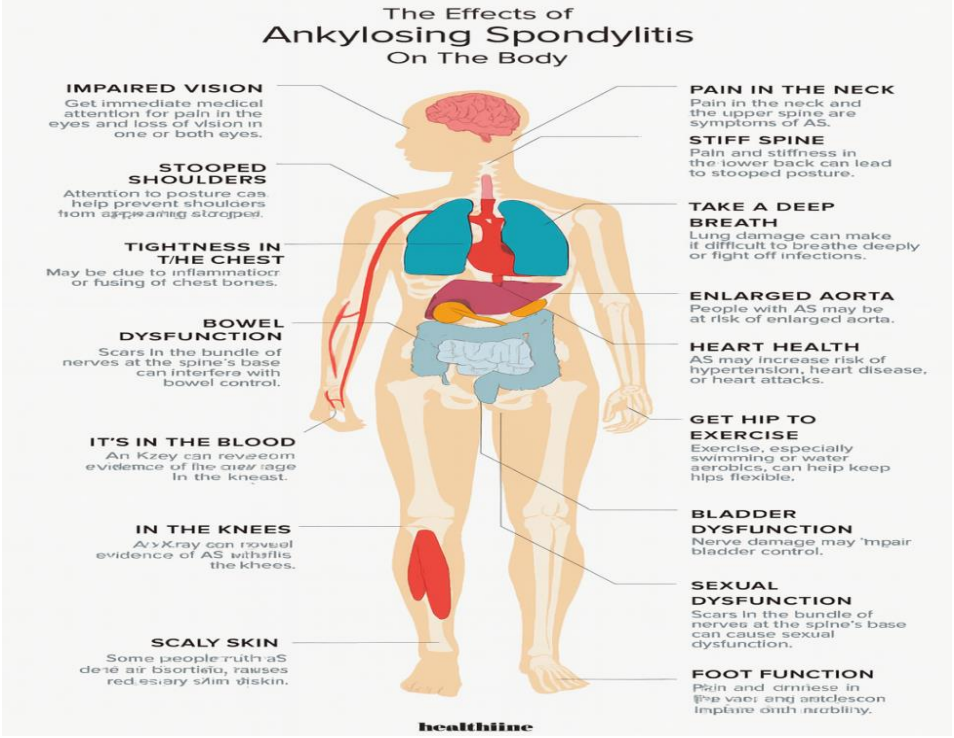

Fig:1 Symptoms Of AS

Genetic treatment of AS

It has been acknowledged that hereditary factors are essential to the development of AS. The link between genetics and AS has been a topic of ongoing debate since hereditary factors in familial AS were confirmed in 1961 [23]. 10 Studies with twins have demonstrated that the concordance rate for monozygotic twins (63%) is much higher than that for dizygotic twins (23%). Genetic effects have been identified as pathogenic factors responsible for over 90% ofthe population variance in AS manifestations. A major genetic factor is the class I allele HLA-B27 of the major histocompatibility complex (MHC) which was identified in 1973 [24].Even though the pathomechanism is not clearly understood HLA-B27 has been linked to the prevalence of AS across various populations globally. Research indicates that 90%–95% of patients with AS are HLA-B27 positive whereas only 1%–2% of individuals with HLA-B27 positivity develop AS. For individuals with an affected first-degree relative this figure rose to 15%–20%. The familial tendency of AS was striking with relative risks of first-degree relatives for second-degree relatives [25]. Besides the connection to AS development patients who are HLA-B27 positive demonstrated a significantly lower average age of onset and a greater occurrence of acute anterior uveitis compared to those who are HLA B27-negative [26].

The polymorphism of HLA-B27 is considerable. To date, more than 100 subtypes have been identified and their prevalence rates vary among different ethnicities, particularly between individuals of East Asian and Caucasian descent. The most common subtypes in AS are HLA-B2705 (found in Caucasian populations) HLA-B2704 (in Chinese populations) and HLA-B2702 (in Mediterranean populations) as reported. In contrast the two subtypes HLA-B2706 and HLA-B2709 do not appear to be linked to AS. Further more genetic factors are not the sole contributors to the development of AS. Research on HLA-B27 transgenic rats regarding β2 microglobulin (β2m) which is a noncovalent component of the MHC-I complex has demonstrated that extra β2m decreases HLA-B27 misfolding and encourages arthritis and spondylitis suggesting that B27 misfolding is linked to intestinal inflammation 26 This finding indicated that abnormal β2m may interact with HLA-B27 in the development of AS a possibility that can be elucidated by protein misfolding theories and will be addressed further in the pathogenesis section. Although HLA-B27 is the genetic factor that has been stressed the most its contribution to AS heritability is only 20%. which shows that there are additional genetic influences on AS [27]. Advancements in genome wide association studies (GWASs) and other technologies have led to the identification of non-HLA-B27 and even non-HLA genes associated with AS in recent years. Additionally the genetic differences among various ethnic groups have been explored and compared during this period. HLA-B60 is associated with HLA-B27-negative AS and elevates the risk of developing the disease by 3 to 6 times. According to an analysis conducted on a Taiwanese population, the interaction of HLA-B60 with HLA-B27 may serve as a more effective marker for AS susceptibility risk. HLA-B7, HLA-B16, HLA-B35, HLA B38 and HLA-B3933 have also been linked to HLA-B27 negative AS across different ethnicities with mechanisms yet to be understood. A study involving 1,000 AS patients and 1,500 healthy individuals reported an initial association and independent validation of two new loci associated with AS ERAP1 (also known as ARTS1) and IL23R in a North American sample. It also provided preliminary evidence for several non-MHC nonsynonymous single nucleotide polymorphisms (nsSNPs) [28].

Microbiological and immunological aspects Of AS

AS is associated with various autoimmune diseases such as IBD, anterior uveitis, and psoriasis, indicating that these conditions may have a shared genetic foundation and involve some common immunological mechanisms [29]. The immune cells and cytokines in AS exhibit differences that imply immunological effects contribute to the pathogenesis of AS. In AS patients and healthy HLA-B27-positive controls the reported levels of T cells secreting tumor necrosis factor (TNF) α and interferon (IFN) were lower in peripheral blood. In AS patients CD8+ T cells tended to produce more IL-10. Other findings have shown immunological influences in the development of AS which is discussed in the next section. Microbialinfection serves as a catalyst for both the host's innate immune system and AS development. In a germ free environment HLA-B27 transgenic rats did not exhibit SpA characteristics. However upon the introduction of commensal bacteria into these models the situation changed indicating potential interactions between HLA-B27 and the microbiome. In AS patients the gut microbiomecomprising Lachnospiraceae, Veillonellaceae, Prevotellaceae, Porphyromonadaceae, and Bacteroidaceaeexhibited significant differences compared to that of healthy controls. Klebsiellapneumoniae functions as an opportunistic pathogen in the normal human gut with research suggesting it could play a role in worsening the autoimmune process of AS .There are controversial findings about the connection between AS activity and the fecal microbiome load including Klebsiellapneumoniae. Certain researchers proposed the hypothesis that there is an indirect influence of Klebsiellapneumoniae on AS development through interactions with HLA B27. Furthermore the infection of the gut microbiome can be attributed to an immune component deficiency which results in heightened and prolonged immune responses [30].

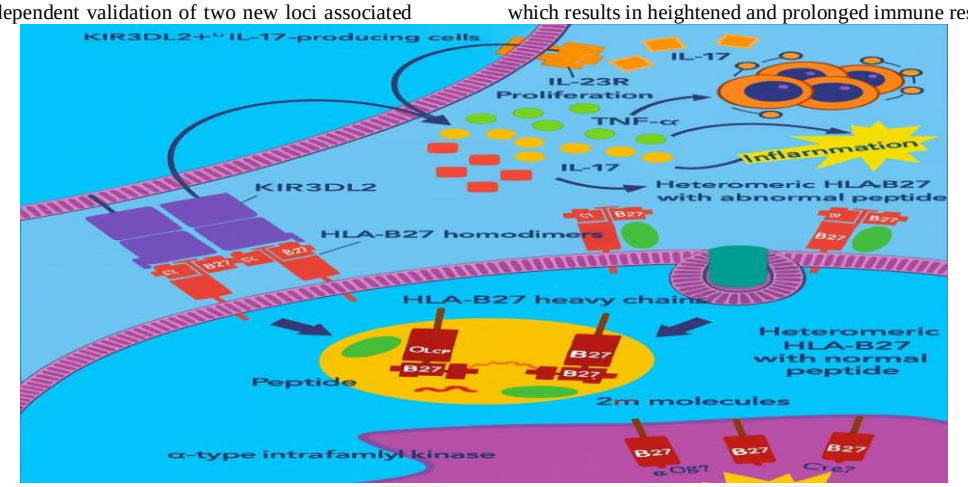

Fig: 2 Various functions of ER resident and cell surface HLA-B27 dimers.

DIAGNOSIS OF AS

Your healthcare professional may inquire about your medical history, family history, and symptoms to diagnose ankylosing spondylitis. Additionally, your healthcare provider may conduct a physical examination to assess your posture, flexibility, and any regions experiencing pain or stiffness. Additionally you might be asked to take a deep breath to check for any difficulties in expanding your chest [31].

X-Ray imaging of AS

X-rays can detect alterations in joints and bones which may indicate ankylosing spondylitis also known as radiographic axial spondyloarthritis. X-ray changes may take years to develop. X-ray images might not reveal early stage disease. MRI employs radio waves and a powerful magnetic field to create more detailed pictures of soft tissues and bones. MRI scans can identify nonradiographic axial spondyloarthritis at an earlier stage of the disease. However the costs of MRI scans are considerably higher [32].

Laboratory procedures

No particular laboratory tests exist to diagnose ankylosing spondylitis. Some blood tests such as the erythrocyte sedimentary rate (sed rate) and C reactive protein (CRP) can detect inflammation markers. However inflammation can be triggered by a wide range of health problems.The HLA-B27 gene can be tested for in blood samples. However numerous individuals with the gene do not develop ankylosing spondylitis. Moreover, individuals lacking the HLA-B27 gene may also have the condition.

Computerized tomography

A CT scan, short for computerized tomography scan is a form of imaging that employs X-ray methods to produce detailed pictures of the body. It then employs a computer to generate cross-sectional images known as slices of the bones, blood vessels, and soft tissues within the body. CT scan images provide more detail compared to standard X-rays. A CT scan can serve various purposes. It serves to diagnose illness or trauma and to devise plans for medical surgical or radiation therapy [33].

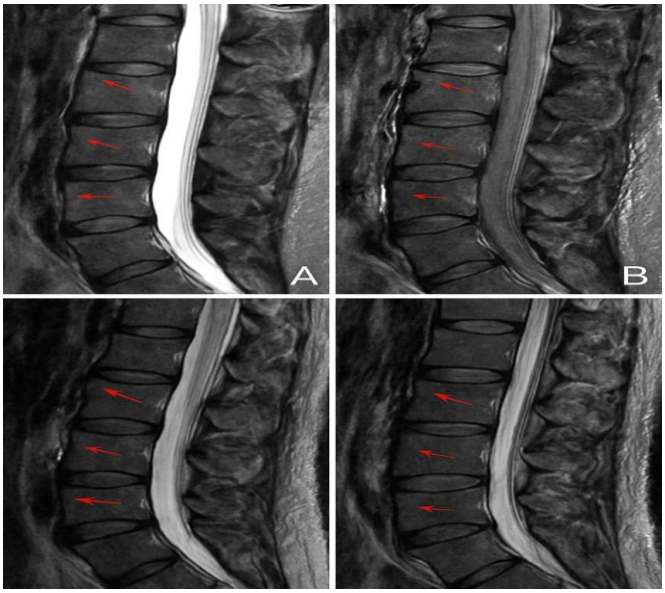

Fig:3 CT Scan of AS

MRI Techniques

Magnetic resonance imaging (MRI) is a medical imaging method that utilizes a magnetic field and computer generated radio waves to produce detailed images of the organs and tissues within your body. The majority of MRI machines are sizable tube like magnets. As you lie in the MRI machine the magnetic field interacts with radio waves and hydrogen atoms in your body to produce cross-sectional images akin to slices of bread. The MRI machine can also create 3D images that allow for viewing from various perspectives.

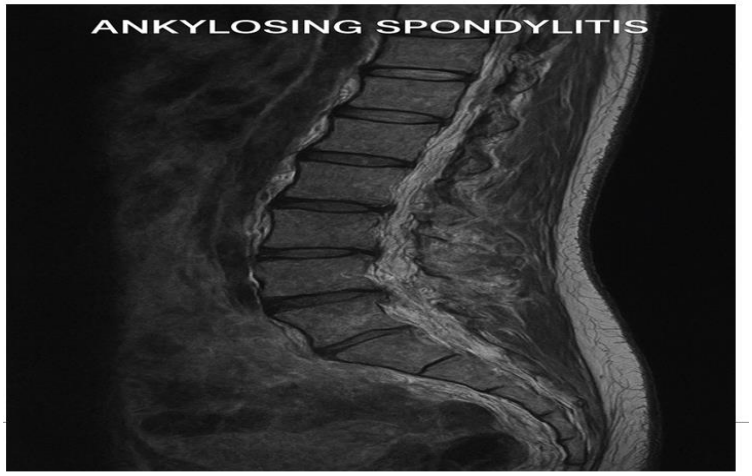

Fig: 4 MRI of Ankylosing Spondylitis

X-ray imaging

An X-ray is a rapid and painless examination that produces images of the internal structures of the body especially the bones. X-ray beams penetrate the body. The absorption of these beams varies according to the density of the material they traverse. Bone and metal which are dense materials appear white on X-rays. Air in the lungs appears black Fat and muscle present themselves as different shades of gray [34].

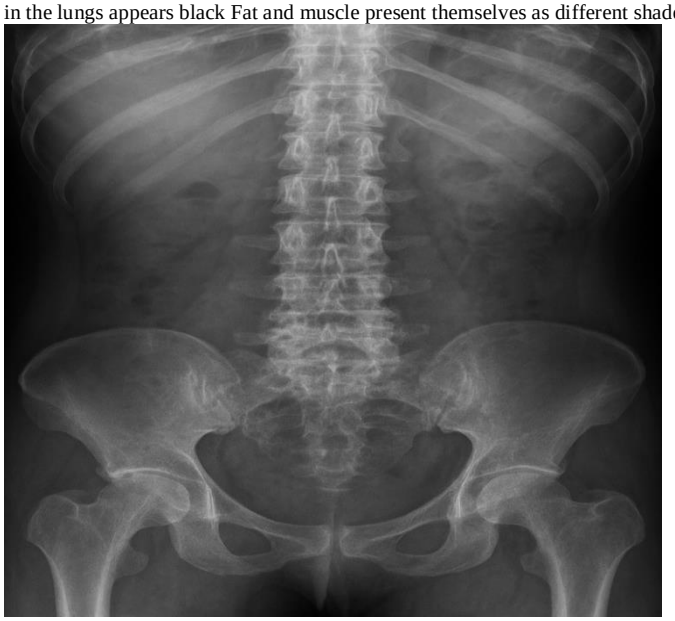

Fig: 5 X-Ray of AS

TREATMENT METHODE FOR AS

Pharmacological interventions

The objectives of AS treatment are to enhance and preserve spinal flexibility and normal posture alleviate symptoms minimize functional limitations and reduce complications [35]. The cornerstones of pharmacological treatment comprise non-steroidal anti-inflammatory drugs (NSAIDs) and TNF-α inhibitors (TNFis) [36]. Further treatments comprise of non-TNFi biologics (such as secukinumab) methotrexate and sulfasalazine. In addition clinical trials suggest that the oral small-molecule JAK inhibitors tofacitinib and filgotinib show promise and may soon receive approval for AS [37]. Expert panels in France, Spain, Turkey, Canada the United Kingdom, the United States and Europe have issued several guidelines for AS management all based on systematic literature reviews [38].

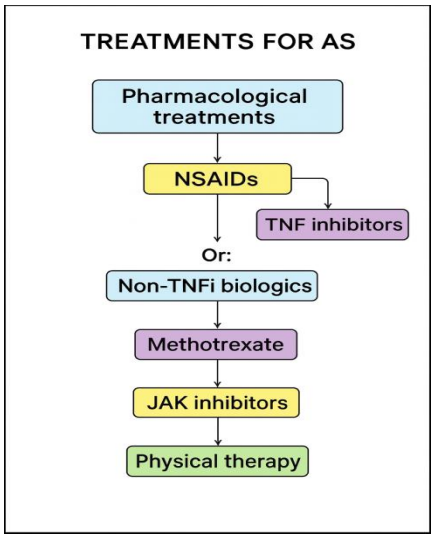

Fig: 6 Treatment of AS

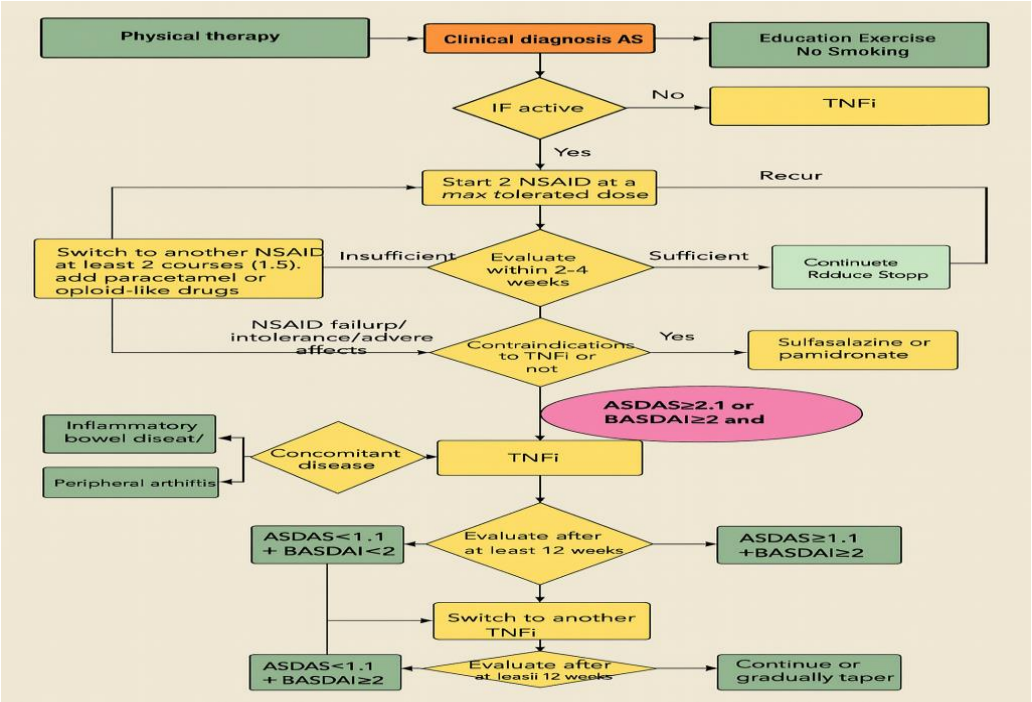

Fig: 7 Drug treatment strategies for ankylosing spondylitis patients

Surgery Methods of AS

In patients with AS who develop severe spinal deformity especially thoracolumbar kyphosis (which affects over 30% of patients) or advanced hip arthritis surgical treatment is considered [40]. The goals of corrective spinal surgery are to restore posture alleviate pain enhance function and prevent the progression of deformity. Nonetheless procedures entail considerable risks such as a 4% rate of perioperative mortality and a 5% incidence of permanent neurological complications [39].Introduced by Smith Petersen in 1945 the Opening Wedge Osteotomy (OWO) aims to correct Over the years various osteotomy techniques have been created to address spinal deformities . lumbar kyphosis by creating a posterior gap. However it is linked to high complication rates due to excessive anterior column tension which can result in vascular and neurological injuries [40]. The Polysegmental Wedge Osteotomy (PWO) initially detailed by Wilson in 1949 and improved upon by Zielke in the 1980s employs several closing wedge osteotomies for a smoother correction and utilizes internal fixation systems like Harrington rods hooks and screws. Regardless of this it has been linked to implant failure rates nearing 40% which leads to diminished patient satisfaction [41]. The Closing Wedge Osteotomy (CWO) first proposed by Scudese and Calabro in 1963 and subsequently refined by Ziwjan and Thomasenentails the excision of a posterior vertebral wedge to enable passive spinal extension. Compared to OWO and PWO this technique offers better correction and fewer complications [42]. Proposed by Kawahara for cervical deformity correction the Closing Opening Wedge Osteotomy (COWO) merges the advantages of both OWO and CWO. It results in a substantial reduction of kyphosis such as from 67° to 18° while enabling safe controlled shortening of the spinal cord and lengthening of the aorta.When neurological deficits are present or worsening or when spinal instability is confirmed surgical intervention for fractures is considered. However when complete paralysis has lasted for several hours surgery usually does not enhance recovery outcomes. Moreover the failure of implants is a recognized issue leading to the need for revision surgery in about 15% of cases[43].

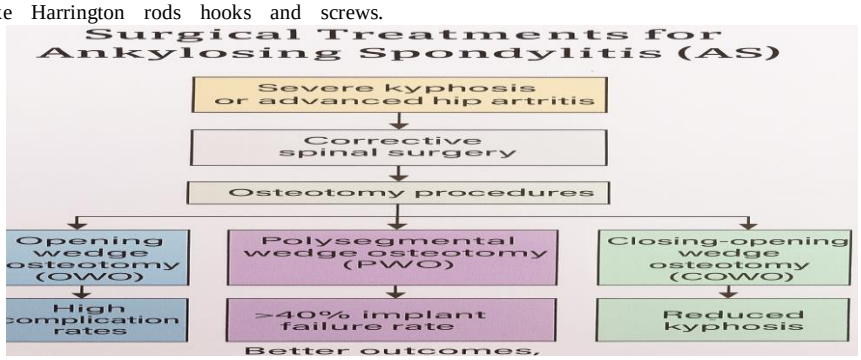

Fig: 8 Surgical treatment

Recommendations for the treatment of different types ofAS

These recommendations adhered to ACR and GRADE methodology as detailed in Supplementary Appendix. Systematic literature reviews were conducted for pre-defined clinical Patient-Intervention-Comparator-Outcome (PICO) questions. An expert voting panel looked at the resulting evidence built recommendations and cast votes on them. Key definitions like in the those for active and stable disease. During the preparation of this manuscript after the voting panel had convened clinical trials involving ixekizumab became accessible. The data from these trials were provided to the voting panel which reviewed and voted on revised recommendations that included ixekizumab [44].

Recommendations for the Treatment of Patients with Active AS.

We provide a conditional recommendation for continuous NSAID treatment rather than on demand NSAID treatment in adults with active AS (PICO).The effectiveness of NSAIDs in alleviating symptoms of active AS has been shown by numerous controlled trials. There is no consistency in the evidence about how continuous use of NSAIDs affects spinal fusion as shown in radiographs over two years in comparison to on demand use. Research on celecoxib showed that ongoing use resulted in reduced progression, whereas a study on diclofenac demonstrated no difference in progression.

Despite the uncertainty regarding their possible disease modifying effects the committee conditionally endorsed the continued use of NSAIDs in patients with active AS primarily for managing disease activity. Whether to use NSAIDs in the long term can vary depending on how severe the symptoms are what the patient wants and whether there are other health issues particularly those that affect the cardiovascular system kidneys or gastrointestinal tract [45].

Recommendations for the Treatment of Patients with Stable AS.

In adults with stable AS we offer a conditional recommendation for on-demand NSAID treatment rather than continuous NSAID treatment (PICO). This recommendation applies to patients who have achieved stability without the use of medication. This group considered the possibility that the toxicities linked to ongoing NSAID treatment could outweigh the uncertain benefit of diminished radiographic progression. When symptoms recur in the short term it is worth considering treatment as needed. We strongly recommend that adults with stable AS continue treatment with the original TNFi instead of being required to switch to its biosimilar (new PICO). The panel noted that while the effectiveness of originator and biosimilarTNFi is comparable and either can be chosen for initiating new TNFi treatment courses there should not be a mandatory switch to a biosimilar during treatment in the absence of evidence supporting interchangeability.Changes in medication can increase the risk of destabilizing a patient. The panel concluded that additional data were needed to understand the frequency of potential issues and concerns arising from switching patients who were stable on an originator TNFi to its biosimilar. Considering these concerns the panel concluded that a robust rationale is necessary for altering medications particularly given the negligible cost savings observed for U.S. patients .

Recommendations for Adults with AS-Related Comorbidities

The basis for these recommendations is mostly made up of indirect comparisons of acute uveitis rates from clinical trials and observational studies rather than direct comparative analyses. A number of studies reported overall rates of uveitis without making a distinction between recurrent and incident episodes. Generally speaking the uveitis incidence was reduced among patients administered adalimumab and infliximab as opposed to those treated with etanercept.

Certolizumab and golimumab can also be regarded as treatment options although the supporting evidence for them is not as strong. Data from clinical trials indicate that the occurrence of uveitis flares in AS patients treated with secukinumab is comparable to that seen with a placebo nevertheless additional investigation is needed. Further moresecukinumab has demonstrated no advantages in the treatment of panuveitis or posterior uveitis. Insufficient evidence makes it unclear how often patients receiving ixekizumab treatment experience uveitis flares

Recommendations for the Treatment of Patients with Active or Stable Non-Radiographic Axial Spondyloarthritis (nr-axSpA)

Patients with nr-axSpA underwent parallel evaluations of pharmacological treatments. However of the research questions no relevant published evidence was available. TNF inhibitors (TNFi) are the only treatment for nr-axSpA backed by high-quality evidence from multiple clinical trials among all therapies.

Evidence from single studies of low to very low quality suggests the following-

•For nr-axSpA, treatment outcomes do not differ significantly among various TNFi.

• After stopping TNFi therapy there is a considerable risk of disease relapse.

• The persistence of TNFi treatment does not increase with co-treatment involving non-biologic medications.As a result the majority of nr-axSpA treatment recommendations were based on data associated with ankylosing spondylitis (AS).The recommendations for AS and nr-axSpA are mostly alike with one key difference.

• For AS patients secukinumab or ixekizumab is strongly recommended as a treatment compared to no treatment.

•The recommendation for nr-axSpA patients is conditional due to the absence of clinical trials assessing these medications in this population [48].

Evaluation parameters of AS

In adults with active AS we conditionally recommend against using the treat to target strategy which aims at a target of ASDAS < 1.3 (or 2.1) over a treatment strategy based on physician assessment (new PICO).The concept of treat to-target strategies is well founded in chronic disease management for conditions that have an accurate measure of disease activity (often one that is asymptomatic as in blood pressure or glycosylated hemoglobin) a tight link between this disease activity measure and future health outcomes and evidence that maintaining a particular target in the disease activity measure is closely associated with better long-term health. Indirect support for the treat to target approach in AS comes from correlations between AS activity levels and future radiographic progression however it lacks strong direct evidence. The panel assessed that more persuasive proof of benefit should exist before supporting this shift in practice as implementing this strategy would impose further burdens on patients and providers. It was feared that concentrating on a particular target might result in some patients undergoing rapid cycling through all treatments currently available. As indicated by the 2015 guidelines measuring disease activity is crucial for informing treatment choices [49].

In adults with AS of unclear activity while on a biologic we conditionally recommend obtaining an MRI of the spine or pelvis to evaluate activity (new PICO) For adults with nr-axSpA of unclear activity who are on a biologic we conditionally recommend pelvis MRI to evaluate activity (new PICO). It can be challenging to determine whether a patient is experiencing inflammation that requires a treatment change as physical and laboratory measures often appear normal despite active axSpA and symptoms may be non specific. There is limited evidence indicating that awareness of MRI findings related to the spine and sacroiliac joints might change treatment recommendations.Nonetheless the extent of inflammatory change observed on MRI may not align with treatment responses and the site of inflammation on MRI may not correspond to the pain location. The panel assessed that MRI could offer valuable insights in situations where disease activity was

uncertain and such information would affect treatment choices. In patients with nr-axSpA imaging should target the sacroiliac jointsWhen interpreting MRI results it is crucial to consider the range and frequency of abnormalities such as bone marrow edema lesions that can occur in individuals without axSpA and may not indicate inflammation due to axSpA. MRI is not advisable for patients who are clearly clinically active or stable or when the results would not be anticipated to alter treatment [45]

Conclusion

Ankylosing spondylitis is an autoimmune disease influenced by multiple factors including significant genetic immunological and microbial contributions. To avert long-term disability structural damage and a decline in quality of life it is crucial to identify issues early and intervene promptly. Although NSAIDs continue to be the first line treatment biologic agents especially TNF-α inhibitors have revolutionized disease management and provide significant clinical benefits particularly in cases of recurrent uveitis or high disease activity. When clinical evaluations lack clarity imaging methods like MRI are crucial for identifying initial inflammatory alterations.

While advanced deformities or spinal fractures may necessitate surgical procedures achieving optimal outcomes relies on careful selection and specialized expertise. It is necessary to continue research in order to gain a better understanding of the processes involved in bone erosion and new bone formation enhance the personalization of treatments, and create therapies that more effectively alter the course of disease. In summary the key elements of AS management are pharmacologic therapy, physical rehabilitation, and patient-centered care.

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