International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 56-61 www.ijprajournal.com ISSN: 2249-7781

Ankylosing spondylitis: etiology, pathogenesis, and treatments

Trupti Ghorpade* Rushikesh Jadhav, Santosh Waghmare, Ashwini Andhale, Dr.H.V. Kamble

NAME OF INSTITUTE: Loknete Shri Dadapatil Pharate Patil College OfPharmacy, Shirur, Pune,412211
Department of Pharmacology

Submitted: 01-01-2022 Accepted: 10-01-2022

ABSTRACT
An interminable type of joint pain what influences for the most part the spine and in many prompting combinations of the vertebrae. Guys have a higher frequency than females 2–3:1 proportion. More youthful age gathering is more affected. This generally influences the pivotal skeleton; however, it might likewise connect with fringe joint pain and extra-articular features. The beginning of the ailment is progressive and portrayed by aseptic aggravation at the sacroiliac joints (SIJs). It causes incapacity and decreased personal satisfaction. The most widely recognized finding of Ankylosing spondylitis (AS) is acute foremost uveitis which is found in 20–25% of patients. Eye and inside issues may likewise occur. The principle side effects in eye are torment, diminished impression of light, photophobia, and expanded lacrimation. The solidness of the influenced joints intensifies after some time. AS is discovered worldwide, however, it is increasingly common in Caucasians. This has a place with spondyloarthropathy class of Rheumatic illnesses. There is no remedy for ankylosing spondylitis. Against - rheumatic medications are less full of feeling and biologic treatments are successful. In a large portion of the cases, medical procedure is the main way. This survey article talked about ankylosing spondylitis, its weight, pathogenesis, conclusion, and the board. Significant progress in its pathophysiology and treatment has been achieved in the last decade. Immune cells and innate cytokines have been suggested to be crucial in the pathogenesis of AS, especially human leukocyte antigen (HLA)-B27 and the interleukin-23/17 axis. However, the pathogenesis of AS remains unclear. The current study reviewed the etiology and pathogenesis of AS, including genome-wide association studies and cytokine pathways.

Keywords: Back pain, Degeneration, Joint pain, Sacroiliitis,Pathogenesis

I. INTRODUCTION

A ceaseless type of joint pain what influences, for the most part, the spine and in many prompting combinations of the vertebrae. Guys have a higher occurrence than females 2–3:1 proportion. More youthful age gathering is increasingly influenced. This generally influences the pivotal skeleton, however, it might likewise connected with fringe joint inflammation and extra-articular features. The beginning of the sickness is steady and described by aseptic irritation at the SIJs. It causes handicap and diminished personal satisfaction. The most widely recognized finding of AS is acute front uveitis which is found in 20–25% of patients. Eye and inside issues may likewise occur. The primary indications in eye are torment, diminished impression of light, photophobia, and expanded lacrimation. The firmness of the influenced joints intensifies after some time. AS is discovered worldwide, however, it is progressively pervasive in Caucasians. This has a place with spondyloarthropathy class of Rheumatic sicknesses. There is no solution for ankylosing spondylitis. Hostile to rheumatic medications are less full of feeling and biologic treatments are compelling. In the greater partof the cases, medical procedure is the main way. This survey article talked about ankylosing spondylitis, its weight, pathogenesis, analysis, and executives(1).Spondyloarthropathy (SpA) refers to a heterogeneous group of rheumatic diseases that present common clinical and genetic features, which are classified as peripheral or axial (axSpA) based on what parts of the body are predominantly affected. Ankylosing spondylitis (AS), a type of SpA, is an autoimmune disease that mainly involves spine joints, sacroiliac joints (SIJs) and their adjacent soft tissues, such as tendons and ligaments. In more advanced cases, this inflammation can lead to fibrosis and calcification, resulting in the loss of flexibility and the fusion of the spine, resembling “bamboo” with an immobile position. The main clinical manifestations include back pain and progressive spinal rigidity as well as

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 56-61 www.ijprajournal.com ISSN: 2249-7781

inflammation of the hips, shoulders, peripheral joints and fingers/toes. In addition, there are extra-articular manifestations, such as acute anterior uveitis and inflammatory bowel disease (IBD). However, these extra-articular manifestations differ between East Asian and Caucasian populations. In a study involving 988 patients with ankylosing spondylitis in east Asia, only 0.4% developed inflammatory bowel disease.[1] However, in some analyses performed in Western countries, ~5%–10% of patients with AS present with inflammatory bowel disease(3).

Classification using ESSG criteria

Inflammatory spinal back pain or synovitis (asymmetric and predominantly in lower extremities)at least one of the following:
(1) Alternating buttock pain,
(2) sacroiliitis,
(3) heel pain (enthesitis),
(4) psoriasis,
(5) inflammatory bowel disease, and (6) urethritis/acute diarrhea in preceding 4 weeks.(1,2).

Etiology

As an autoimmune disease, AS develops through complex interactions between genetic background and environmental factors. Although significant progress has been achieved in the past decades, the etiology of AS remains unclear to some extent. To date, studies have revealed some factors that may be related to the occurrence of AS, including genetic background, immune reaction, microbial infection, and endocrinal abnormity.

Diagnosis

The finding of AS is made dependent on the altered New York criteria 1984.
Basic Criteria
• Low back agony and solidness for longer than 3 months, which improve with exercise but are not diminished by rest
• Limitation of movement of the lumbar spine in both the sagittal and frontal planes
• Limitation of chest extension when contrast with typical qualities which was associated with age and sex.

Radiological Criteria

1. Sacroiliitis grade
2 reciprocal or evaluation
3–4 unilateral(4).
• 0 = ordinary
• 1 = suspicious changes
• 2 = least variation from the norm (little limited zones with disintegrations or sclerosis)
• 3 = unequivocal variation from the norm (moderate or progressed sacroiliitis with disintegrations, proof of sclerosis, extending, narrowing, or halfway ankylosis)
• 4 = serious variation from the norm (complete ankylosis(4).

Immunological and microbial factors

AS is related to a series of autoimmune diseases, including IBD, anterior uveitis and psoriasis, which suggests that they may share a genetic basis and some common immunological processes. The differences observed in immune cells and cytokines in AS suggest the role of immunological effects in AS pathogenesis. In the peripheral blood of AS patients and healthy HLA-B27-positive controls, the levels of T cells secreting tumor necrosis factor (TNF)-α and interferon (IFN)-γ were reportedly lower. CD8+ T cells in AS patients tended to secrete more IL-10(5). Other findings have also demonstrated immunological influences in AS development, which is discussed in the following section.

Microbial infection acts as a triggering factor of the host innate immune system and AS development(6) HLA-B27 transgenic rats failed to develop features of SpA in a germ-free environment, which changed when commensal bacteria were introduced into the germ-free models(7,8) suggesting possible interactions between HLA-B27 and the microbiome. The gut microbiome,
including Lachnospiraceae, Veillonellaceae, Prevot ellaceae, Porphyromonadaceae,
and Bacteroidaceae, showed significant differences in AS patients compared with that in healthy controls(9).Klebsiella pneumoniae acts as an opportunistic pathogen in the normal human gut, and studies have suggested that it may be an exacerbating agent in the autoimmune process of AS(10). Controversial results exist regarding the relationship between the fecal microbiome load, such as Klebsiella pneumoniae, and AS activity. Some scientists hypothesized that Klebsiella pneumoniae influences AS development indirectly through interplay with HLA-B27(11). In addition, gut microbiome infection is partly due to the relative deficiency of immune components, leading to immune responses of a higher intensity and longer duration(12).

Pathogenesis

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 56-61 www.ijprajournal.com ISSN: 2249-7781

MHC genetics

The human MHC, also called the HLA complex, belongs to the cell-surface proteins acting in the process of acquired immunity. There are three subgroups in the MHC gene family: class I, II, and III. MHC class I encodes HLA-A, HLA-B, and HLA-C and is present on all nucleated human cells and platelets, presenting epitopes to T cell receptors (TCRs) on the surface of cytotoxic T lymphocytes (CTLs).The heterodimer MHC class I subgroup consists of a polymorphic heavy chain. The chain contains three domains, i.e., α1, α2, and α3. The α1 domain links noncovalently with the non-MHC molecule β2m, while α3 spans the plasma membrane and interacts with the CD8 coreceptor of T cells.The MHC class I complex can link to peptides of 8–10 amino acids in length via one cleft spaced by both α1 and α2, leading to the initiation and propagation of immune responses.A stable MHC molecule needs to be properly packaged and then folded in the cell organelle endoplasmic reticulum (ER) under guidance of chaperones (calreticulin and tapasin)(13).

HLA-B27

HLA-B27, basically belonging to the MHC-I surface protein encoded by the MHC B gene on chromosome 6, is the most essential gene that predisposes an individual to AS. HLA-B27 presents peptide antigens to T immunocytes of the human body defense process and is considered to be significantly linked to AS and associated inflammatory diseases. A study reviewed over 7500 endogenous peptides presented by the eight most frequent HLA–B27 allotypes (HLA–B2702 to HLA–B2709), suggesting that consensus-binding and selection motifs showed significant similarities and differences between various HLA–B27 allotypes.The connection between HLA-B27 and AS has not yet been fully elucidated, although it is widely accepted that the entire intracellular process of HLA-B27 formation needs to be considered. There are some prevailing theories regarding the mechanism, including the hypothesis of arthritogenic peptide, misfolding hypothesis, the hypothesis of molecular mimicry, as well as the hypothesis of the cell-surface HLA- B27 homodimer(14).

Pharmacological treatments

The aims of treating AS are to improve and maintain spinal flexibility and normal posture, relieve symptoms, decrease functional limitations, and reduce complications. The mainstays of pharmacological treatment involve nonsteroidal anti-inflammatory medications (NSAIDs) and TNF-α inhibitors (TNFis). Additional treatments include non-TNFi biologics (secukinumab), methotrexate, and sulfasalazine. Furthermore, the oral small molecule JAK inhibitors tofacitinib and filgotinib appear promising in clinical trials and may soon be approved for AS(15).

Surgical treatments

Untreated AS can cause spinal deformity, with more than 30% of AS patients suffering from thoracolumbar kyphosis. Corrective osteotomy and stabilization are very common in surgical procedures and are recommended under certain conditions, such as adult patients suffering severe kyphosis or advanced hip arthritis. This procedure has a perioperative mortality rate of 4% and permanent neurologic sequelae rate of 5%(16).This surgery is confirmed to contribute to preventing the natural processes of progressive deformity, reducing pain caused by muscle fatigue, improving disability, restoring the global balance and horizontal axis of view, and improving respiratory and digestion function.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 56-61 www.ijprajournal.com ISSN: 2249-7781

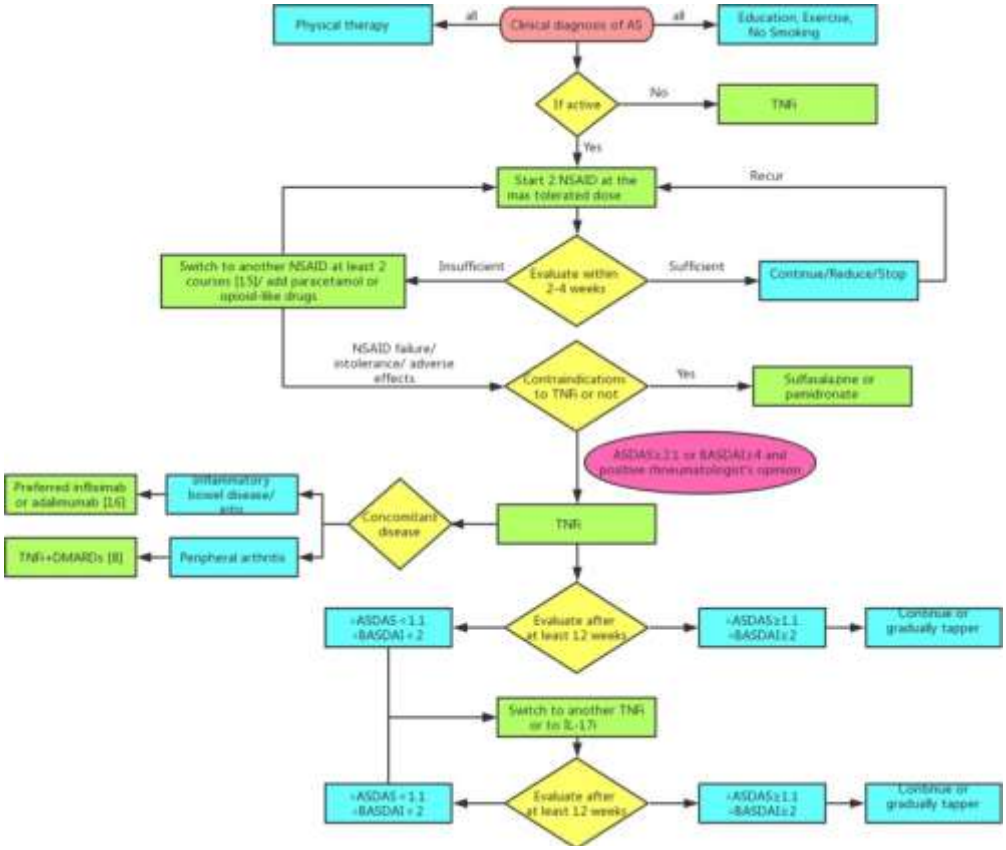

Fig 1. Treatment for AS

Contraindications/Precautions for Treatment

• There was an extraordinary danger of crack in intertwined osteopenic spine and the specialist ought to be with outrageous alert when endeavoring to assemble an AS spine

• Previously, numerous years AS was dealt with adequately with spinal radiation, however, which has the high danger of getting tumors, forexample, myeloid leukemias, and hematologic malignancies(17).

Drugs

• N S A I D s + I N D O M E T H A C I N - b e s t +SULFASALAZINE - helpful for treating fringe joint pain

• First-line treatment for patients with AS with agony and solidness

• Anti-TNF drugs – infliximab or etanercept has been amazingly fruitful and demonstrate a 60% decrease in the bath ankylosing spondylitis disease activity index

• NSAIDs are lacking, which are contraindicated, and are inadequately endured. Be that as it may, analgesics, for example, acetaminophen and opioids, are better utilized for agony control

• Corticosteroid infusions are commonly given as coordinated to the nearby side of musculoskeletal aggravation. The utilization of foundational corticosteroids is not bolstered by proof

• Anti-TNF treatment ought to be given to patients with industriously with high ailment movement, regardless of traditional medicines as indicated by the ASAS proposals. There is no proof to help the compulsory utilization of DMARDs previously, or associative with, hostile to TNF treatment in patients with hub malady

• There is no proof for the viability of illness altering hostile to rheumatic medications (DMARDs), including sulfasalazine and methotrexate, for the treatment of hub malady(18).

II. CONCLUSION

Ankylosing spondylitis is a painful and debilitating disease, with considerable socioeconomic burdens. The pathogenesis of AS is very complex. Current studies suggest that it may be the result of a variety of complicated mechanisms. In the pathogenesis of AS, In particular, the IL-23/IL-17 pathway plays a crucial role in the development of the disease. At present,

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 56-61 www.ijprajournal.com ISSN: 2249-7781

the pathogenesis of AS is considered to mainly involve immune T cells, while B cells are also slightly involved. There are some studies on the pathogenesis of AS mediated by B cells, and related studies may be strengthened in the future. Alternatively, researchers may continue to explore the correlation among cytokines and immune cells and diseases to predict the occurrence, development and severity of disease. Although the pathogenesis of ankylosing spondylitis is not yet clear, the existing research results can have a certain guiding significance for clinical practice.he treatment of AS is mainly composed of drug and surgical treatment. In clinic, NSAIDs and TNF-alpha inhibitors are the main drugs for AS. Moreover, interleukin receptor blockers and some drugs that inhibit new bone formation have received increased attention and become the focus of future research, including IL-6 receptor inhibitor sarilumab and Wnt signal pathway inhibitors. Once AS is not effectively controlled, more severe deformities may appear, and surgical treatment is needed. For severe spinal deformities, spinal surgery is required. For sacroiliac joint lesions, total hip arthroplasty is needed. Treatment of AS has always been the center of research all over the world.

REFERENCES

[1]. Farrouq M, Phiip H. Psoriatic arthritis: A review. EMJ Rheumatol2016;3:114-7
[2]. Benedek TG. The first reports of Dr. Hans Reiter on reiter's disease. J Albert Einstein Med Center1969;17:100-5
[3]. Wang C-R, et al. Rare occurrence of inflammatory bowel disease in a cohort of Han Chinese ankylosing spondylitis patients- a single institute study. Sci. Rep. 2017;7:13165–13165. doi: 10.1038/s41598-017-13573-z. [P
[4]. Amra A, Kenan B, Sezgin S, Ozgur K. Juvenile spondyloarthropathies. CurrRheumatol Rep 2016;18:55.
[5]. Rudwaleit M, et al. Low T cell production of TNFalpha and IFNgamma in ankylosing spondylitis: its relation to HLA-B27 and influence of the TNF-308 gene polymorphism. Ann. Rheum. Dis. 2001;60:36–42. doi: 10.1136/ard.60.1.36.
[6]. Sieper J, Braun J, Kingsley GH. Report on the fourth international workshop on reactive arthritis. Arthritis Rheum. 2000;43:720–734. doi: 10.1002/1529-0131(200004)43:4<720::AID-ANR2>3.0.CO;2-8.
[7]. Taurog JD, et al. The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats. J. Exp. Med. 1994;180:2359–2364. doi: 10.1084/jem.180.6.2359.
[8]. Rath HC, et al. Normal luminal bacteria, especially Bacteroides species, mediate chronic colitis, gastritis, and arthritis in HLA-B27/human beta2 microglobulin transgenic rats. J. Clin. Invest. 1996;98:945–953. doi: 10.1172/JCI118878.
[9]. Costello ME, et al. Brief report: intestinal dysbiosis in ankylosing spondylitis. Arthritis Rheuma. 2015;67:686–691. doi: 10.1002/art.38967.
[10]. Gomez-Simmonds A, Uhlemann AC. Clinical implications of genomic adaptation and evolution of carbapenem-resistant Klebsiella pneumoniae. J. Infect. Dis. 2017;215:S18–S27. doi: 10.1093/infdis/jiw378.
[11]. Zhang L, et al. The association of HLA-B27 and Klebsiella pneumoniae in ankylosing spondylitis: a systematic review. Micro. Pathog. 2018;117:49–54. doi: 10.1016/j.micpath.2018.02.020.
[12]. Sieper J, Braun J. Pathogenesis of spondylarthropathies. Arthritis Rheum. 1995;38:1547–1554. doi: 10.1002/art.1780381105.
[13]. Madden DR. The three-dimensional structure of peptide-MHC complexes. Annu. Rev. Immunol. 1995;13:587–622. doi: 10.1146/annurev.iy.13.040195.003103.
[14]. Schittenhelm RB, Tc LKS, Wilmann PG, Dudek NL, Purcell AW. Revisiting the arthritogenic peptide theory: Quantitative not qualitative changes in the peptide repertoire of HLA-B27 allotypes. Arthritis Rheuma. 2015;67:702–713. doi: 10.1002/art.38963.
[15]. Allouch H, Shousha M, Böhm H. Operationenbeiankylosierender spondylitis (morbus bechterew) Z. Rheumatol. 2018;76:848–859. doi: 10.1007/s00393-017-0400-7.
[16]. Qian BP, Mao SH, Jiang J, Wang B, Qiu Y. Mechanisms, predisposing factors, and prognosis of intraoperative vertebral subluxation during pedicle subtraction osteotomy in surgical correction of thoracolumbar kyphosis secondary to

ankylosing
spondylitis. Spine. 2016;42:E983–E990.
doi: 10.1097/BRS.0000000000002015.

[17]. Imboden J, Hellmann DB, Stone JH. Section II rheumatoid arthritis and spondyloarthropathies. In: Current Rheumatology Diagnosis and Treatment. Spondyloarthropathies. 1st ed., Ch. 18. United States of America: The McGraw-Hill Companies, Inc.; 2004.

[18]. Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. Disorders of immune-mediated injury. In: Harrison's Principles of Internal Medicine. Disorders of the Immune System, Connective Tissue, and Joints. 16th ed., Vol. 13. Ch. 305. United States of America: The McGraw-Hill Companies, Inc.