IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 5 Ser. 1 (May. 2019), PP 01-13
www.iosrjournals.org

Recent Insights in Ankylosing Spondylitis

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ABSTRACT: *Ankylosing spondylitis (AS) is a chronic inflammatory immune-mediated arthritis belongs to the so called group of axial spondylarthritis (SPA) (1).Considerably, the onset of the disease occurs in patients between the third and the fourth decade of life, and if not treated effectively it can lead to disability in about third of the patients (2–6). The pathogenesis of AS is multifactorial and results from a complex interplay between genetic predisposition and environmental triggers (7)HLA B27, from its discovery in 1973,(8) represents the central genetic factor related to disease etiopathogenesis. However, about 10-20% of defined AS patients were HLA B27 negative(9).We aimed in this review to assess the role of different factors contribute to the outcome of the disease.*

Keyword: *Ankylosing Spondylitis, Spondyloarthropathy, HLA B27.*

Date of Submission: 18-04-2019 Date of acceptance: 04-05-2019

I. Introduction

Ankylosing spondylitis (AS) is a chronic immune-mediated inflammatory arthritis belongs to the so called group of axial spondylarthritis (SPA) (41). This group of SpA characterized by their strong association with HLA B27 antigen and involvement of the axial skeleton.AS is the major disease in this group and defined clinically by inflammatory back pain but also it could affect other sites like enthesitis, peripheral arthritis, dactylitis ,and extra articular manifestations as psoriasis , uveitis , inflammatory bowel disease(IBD).Considerably, the onset of the disease occurs in patients between the third and the fourth decade of life, and if not treated effectively it can leads to disability in about third of the patients (42–46).HLA B27, from its discovery in 1973,(47) represents the central genetic factor related to disease etiopathogenesis. However, about 10-20% of defined AS patients were HLA B27 negative (48). This antigen becomes one of the two central arms for the diagnosis of AS in the new classification criteria for ax-SPA settled by The Assessment of the Spondylarthritis International Association (ASAS) (49) which depend on finding of sacroiliitis on imaging with one additional SPA feature (imaging arm) or HLA B 27(human leucocyte antigen B27) positivity with additional two SPA features(clinical arm) in chronic low back pain patients less than 45 years old at onset of symptoms(50). In spite of ongoing research ,The pathogenesis of AS is not fully understood and the exact way by which HLA B27 affect the disease is not clear(41) in addition patients with AS vary in their clinical features and response to treatment(51).Previous studies suggest a relationship between HLA B27 and a younger age of onset ,family history and axial manifestations and less prevalence of Inflammatory Bowel Disease (IBD) and psoriasis (52,53) .We aimed in this review to assess the role of different factors contribute to the outcome of the disease

Prevalence:

In the past AS was considered as a disease of young men only. More studies showed a female affection with male to female ratio 2 or 3 :1, regardless of the presence of significant ethnic and geographical variations. AS has an evaluated prevalence of about 0.5% .in the Caucasian population while the evaluated prevalence of SPAs as agroup is about 1.5% to 2% .(4) human leucocytic antigen (HLA B 27) is commonly associated with susceptibility of the disease and there is a strong connection between the frequency of many subtypes of this allele and the prevalence of AS in a population(10).In the central European population the presence of HLA B 27 is about 6-9 %.(11) While, central and south African population or in Japanese the prevalence is 1% or less leading to low AS prevalence(12). Nevertheless , AS can occur in the absence of HLA B27 and 10 % only of positive HLA B 27 twins who are HLA B27 positive can be inconsistent with the disease incidence and severity(13) .As a result of this strong association, the new ASAS classification criteria for axial SPAs Considers HLA B 27 as an essential feature in the diagnosis.(3,14).

Pathogenesis

The pathogenesis of AS is multifactorial and occurred from a compound interplay between environmental triggers and genetic predisposition(15)while the exact way by which HLA-B27 begins AS is still not clear , and, after many years, we still investigate the evidence to some of the earliest hypotheses. The main hypothesis, the 'arthritogenic peptide theory',proposed that a cell-mediated immune reaction could be initiated by presenting of either bacterial peptides by HLA-B27 or self-mimicking HLA-B27-binding peptides from certain bacteria could initiate leading to AS .(1) The second hypothesis is the 'unfolded protein response', which indicated that the tendency of HLA-B27 to be accumulated in the endoplasmic reticulum, acting as atrigger producing a stress response that results in release IL-23 release(16)while, these two theories have been disputed by a new study, claiming that there is a necessity to reassess the arthritogenic peptide theory according to quantitative changes concerning self-peptide presentation and selection of T-cell. It also reported that the constant binding predilection of HLA-B27 allotypes are not enough to explain the association of the disease.(17)

'HLA-B27 homodimer model' hypothesis is the third one , which favors that there is abnormal reaction of HLA-B27 homodimers with CD4 T cells and natural killer (NK) .Different from the heterodimeric form of HLA-B27, the homodimer can bind to certain killer cell immunoglobulin-like receptors (KIRs), which have expression on NK cells and T cells, causing IL-171 release (18–20).It was proven by Ridley et al(21) that CD41 T cells adjust the KIR-3DL2 expression on the cell surface and that the linking of HLA-B27 to this receptor stimulate T-cell survival and Th17 cell differentiation. Th17 cells are a type of T-helper lymphocyte that produces IL-17(22), a cytokine able to stimulate immune cells such as fibroblasts and macrophages and increase T-cell priming potentiating the release of IL-6, TNF-α, and other chemokines(23).

IL-23 is founded to be one of the triggers of the Th17 response by Oppmann et al(24) This molecule is a cytokine which have proinflammatory properties that appear to be essential in stabilizing Th17 cell phenotype by the transcription factor Blimp-1 (Prdm1)(25), that is linked with Crohn's disease(26). The common site for Th17 cells are in the intestinal lamina propria of the gut (27) and can be in stabled by certain bacteria exposure, resulting in the transition of Th17 cells into regulatory T (Treg) cells(28). Maxwell et al.(29) also reported that IL-23 potentiate the aggregation of Treg cells in the bowel, some of which probably were Th17 previously(30)

Genetics:

The genetic component plays an important role in the etiology of SPA by the HLA-B27 allele (31). That is why AS considered to be an inherited disease as 90 % of theSusceptibilitydepend on genes(1). Despite, the HLAB27 allele considered to be responsible for only 20% of the genetic effect (9) Other alleles, especially HLA-B, are considered to be paly an obvious role in the disease: HLA-B*40:01, HLA-B*47, HLA-B*13:02 and HLA-B*51 are some examples(32). The most significant discovery of the last three years has been that, The risk of developing AS increased with the interaction of ERAP, the protein endoplasmic reticulum aminopeptidase 1 with HLA-B alleles. The major variant of the gene (rs30187, K528R) reacts only with the HLA-B27 allele, and in HLA-B27 negative patients, ERAP1 reacts with the HLA-B40 allele4. The mechanism by which the risk increased remains not obvious; However , it is known that the existence of this gene is not associated with the radiographic severity of the disease(33).A new study showed that when the TLR7 gene copy number is low ,it act as a marker for tendency to AS in males but proceed as a protective factor in women.(1) It was reported by **Ruan et al.**(34) that that genetic polymorphisms of IL-6R (rs4129267) and IL-12B (rs6871626) were linked with more risk of AS whatever of the gender and also could work as markers for diagnosis and prognosis.Recently, multiple other genetic factors of tendency have been discovered, the majority of them through genome-wide association studies (GWAS). Nevertheless, a small fraction of disease predisposition explained by these factors. Although we do not have an overall picture of the genetic basis of SpA, GWAS hits have increased our knowledge of SpA pathogenesis, notably by showing several considerable ways involved in the disease(31).

GWAS have shown the involvement of the T helper 17/23 (Th17/23) axis and its multiple genetic polymorphisms not only in AS but also in psoriasis and inflammatory bowel disease (IBD), increasing the believe of the hypothesis that there is a common pathogenic mechanism and that the development of the disease seems to show implication of microbiome(31).Gene expression profiling can give us more information on the genetic architecture of SpA with a more functional opinion. The recent possibilities offered by high-throughput RNA sequencing technologies, specially in sorted cells, are very hopeful. Functional genomics will also assist in establishing molecular mechanisms underlying genetic associations. Theevenual aim is to drive translational advances resulting in a more efficient diagnosis and treatment of disease(31).

HLA-B27

In the early 70's was the first time to report the association between HLA B27 and AS and after that it was confirmed in other subtypes of the disease.HLA B27 is very variform with multiple hundreds of subtypes identified. The link between it and SPA have been settled for most Frequent subtypes, i.e., HLA-B∗27:05,the

original allele which other subtypes are derived from, B∗27:02, B∗27:04, and B∗27:07(31).Another two subtypes B∗27:09 (a rare subtype found in Sardinia) and B∗27:06(a common subtype in South-East Asia) are of special interest as they were informed to be with less or no association with SPA. (35)The other subtypes are rare so it is difficult to determine their association with SPA. However , the mechanism of the association between HLA B27 and AS is still unknown and many theories were suggested to explain it ,but it is considered to be the main genetic factor predisposing to SpA(36).

Gender differences :

In the last few years there is an evidence suggests that AS involves men and women differently. in a study made by.Landi et al (37) which analyzed 2,044 patients with AS and reported that disease initiates earlier in men but that usually the diagnosis is more delayed than in women. Men have lower disease activity estimated by Assessment of Spondylarthritis international Society (ASAS)-endorsed Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and a preferable quality of life (Ankylosing Spondylitis Quality of Life Questionnaire, or ASQol) but have more bad spinal mobility (Bath Ankylosing Spondylitis Metrology Index, or BASMI) and a more sever radiologic deterioration(Bath Ankylosing Spondylitis Radiology Index, or BASRI). On the contrary, women usually have more peripheral arthritis and an increased predominance of arthritis, enthesitisand dactylitis associated with a worse response to anti-TNF treatment and a worse quality of life (38). This conflict the results suggested by Webers et al.(39), who reported that men had a better quality of life and more radiographic damage but did not detect variations in the activity of the disease or physical function. However, this study includes only 216 patients.

Clinical picture:

Inflammatory back pain considered to be the most characteristic clinical manifestations of AS(5).It is important to differentiate inflammatory from noninflammatory causes of back pain as its occurrence is not infrequent in general population. Inflammatory back pain is characterized by increasing the pain and stiffness in the morning or after long periods of inactivity "gell phenomenon"and decreasing with exercise.patients usually suffered from difficulty sleeping or pain that is not relived by rest or alternating buttock pain(40) . A more specific feature of inflammatory back pain is the alternating buttock pain which represent most probable sacroiliac involvement.sometimes patients represent either pain in the cervical region ,mid thorathic or chest wall which appear as initial manifestations and occurs more commonly in women rather than commonly occurred low back pain(40). other indicative to inflammatory back pain is the significant response to nonsteroidal anti-inflammatory drugs. The occurrence of inflammatory back pain alone is not enough for the diagnosis of AS but increase suspicion of axial spondylarthritis(ax SPA) .(4)As aresult of the inflammation structural damage to the axial skeleton occured and further leads to limitation of the spinal motility .This limitation can measured by the application of settled methods (such as the modified Schober test for measurement of lumbar flexion)(41)(42).

As regard peripheral manifestations the arthritis which appear as general swollen and tender joints as well as enthesis's that appear as inflammation of the site of the insertion of the ligament , tendon or capsule into bone are the most common ones (found in about 30 % to 50 % of patients with ax SPA).This manifestations occurs commonly in the lower limbs asymmetrically , it may be occur at any stage of the disease . One of the other peripheral manifestations is dactylitis that is appear as swelling of the fingers and toes as aresult of tendon-vaginitis.(43)

Generally disease activity is measured by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)(44) or the Ankylosing Spondylitis Disease Activity Score (ASDAS)(45) both of this scores are combined scores ,ASDAS contains an acute phase reactant commonly used is CRP as well as the outcome indices reported by the patient.Moreover the presence of certain known associated conditions like psoriasis ,inflammatory bowel disease and uveitis in apatient with inflammatory back pain make the diagnosis of ax SPA more likely .so it is important to notice and combine all this clinical features for an early diagnosis of AS or any other type of ax-SPA(4).Uveitis is the most common extra-articular manifestation and presents typically as uveitis anterior it is characterized by acute onset ,short duration ,unilateral direction and frequently alternating from one eye to the other . while psoriasis and inflammatory bowel disease are less frequent extra articular manifestation(46–48) .Other extra articular manifestation include cardiovascular disorders. The well recognized cardiac diseases related to AS- include aortic regurgitation, aortitis, and atrioventricular conduction disturbances [46–50]. Now, however, the field of cardiovascular diseases associated with AS has become wider. Cardiomyopathy, atherosclerosis, left ventricular dysfunction,coronary arterydisease (CAD) cardiac arrhythmias and congestiveheartfailure(CHF). especially, are being mentioned more considerably.(49)

Inflammatory chest pain considered to be the most common thoracic manifestation in AS patients as the cost sternal and costovertebral joints and insertion muscles are involved. With progression of the disease,

pulmonary function tests usually reveal reduced vital capacity and total lung capacity and increased residual volume and closing volume-to-vital capacity ratio restriction of the thoracic cage can be identified (49).

Coexistence of AS with other autoimmune diseases:

Elevated IgA level is a common finding in the serology of AS patients, and IgA nephropathy, IgA multiple myeloma and Henoch–Schölein purpura, have been reported in AS patients(49)(50).Occurrence of AS with Behcet'sdisease , Sjogren's syndrome, autoimmune thyroid disease, rheumatoid arthritis, adult-onset Still's disease and mixed connective tissue disease, have also been reported.(49).

Assessment of the disease activity:

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (51)is the most common used agent to measure the activity of the AS .while,it show some limitations including its dependence on the patient point of view and that its responsiveness is doubtful(52,53) .If the patient has a score exceeds 4 he considered to be in activity. Furthermore,less subjective variables such as CRP ,are less sensitive to the disease activity (54). the Ankylosing Spondylitis Disease Activity Score (ASDAS) was suggested by International Society of Spondylarthritis (ASAS) as a new score to assess the disease activity(55,56).ASDAS is a combined index,joining the patient outcome measures with acute phase reactants.It involve BASDAI questions number 2(pain) , 3 (swelling)and 6(stiffness) of BASDAI plus CRP and patient global assessment (PGA). By this combination of other parameters to the patient assessment. The ASDAS is expected to show more correlation with the physician assessment.

The cutoff points of the ASDAS suggested by ASAS (<1.3 inactive disease, 1.3–2.1 moderate activity, 2.1–3.5 high activity, and >3.5 very high activity) vary from those noticed when using the minimally acceptable clinical status of the patient(57).Bath Ankylosing Spondylitis Functional Activity Index (BASFAI) is used to evaluate (58) physical functioning in ankylosing spondylitis patients .It is the most commonly used functional index for evaluating patients with AS, primarily in studies of disease impact and in clinical trials(59).

Diagnosis:

In the majority of patients, the first symptomof SPA (usually inflammatory back pain) occurs in the third or fourth decade of life but the inflammatory back pain is not enough to reach a diagnosis, it needs a composition of clinical signs and symptoms with the radiological evaluation of sacroiliitisto reach an AS diagnosis.

Clinical Diagnosis

Special tests:

The following estimation are used to detect spinal involvement,

(1)"occipt to wall distance" is measured to estimate the cervical spine mobility, (2)"modified schoper test" used to estimate anterior lumbar spinal flexion,

(3)" lateral mobility" of the spine is measured by using lateral bending of the lumbosacral spine .

(4)" chest expansion" is measured from the lower border of the xiphisternum to estimate the rib cage motion.Also, palpation or percussion of the sacroiliac joint may show tenderness but actually it is not a reliable sign for the presence of sacroiliitis.Applying pressure on the sacroiliac join by abduction, flexion and external rotation maneuver and Gaenslen test could clarify dysfunction of sacroiliac joint and may also produce pain. However,these tests are nonspecific.

Examination of the eye, cardiac system,pulmonary system and the skin can clarify extra articular manifestations (4).

Radiological Diagnosis:

Sacroiliitis is the first and required radiographic manifestation of AS,Therefor pelvic radiograph is fundamental to make the diagnosis of AS. The radiographic grades of AS are 5 grades from 0=normal to IV=complete ankylosing. The standard anteroposterior view radiograph of the pelvis may not allow good visualization of the sacroiliac joint (SI) joints Due to the oblique direction of the SI joint.Ferguson view may overcome this problem by a 30 degree cephaled angel view of the sacroiliac joint.visualization of the hip joint can be also allowed by pelvic x-ray as they are commonly affected in AS."Squaring of the vertebral bodies" is a substantial radiological sign caused by osteitis and later erosion of the anterior superior and inferior surfaces of the spine(60).The characteristic bony protuberances which called "syndesmophyte" are produced from ossification of the spinal ligament which connect the intervertebral discs.

In late and longstanding stages of AS this syndesmophyte enlarges and fuse together to form the characteristic appearance of "bamboo sign".According to the modified New York criteria for the diagnosis of AS it required for the patient to have x ray sacroiliitis (defined as bilateral grade 2 or unilateral grade

3)(4).Nevertheless , there is a difficulty in the interpretation of the X-ray and this give a field for interpretational differences especially in early phases of the disease. The diagnosis of AS needs x-ray evidence of sacroiliitis and due to this requirement the diagnosis may be delayed up to 10 years(61,62) This of great importance as delaying the diagnosis may lead to sever morbidity and also delaying appropriate treatment. CT and MRI showed a higher sensitivity in detecting sacroiliitis in an early stage of AS(63).CT appears to be better than MRI in detecting of chronic bony changes (64).While MRI is the only technique that visualize the chronic bony changes simultaneously with acute inflammatory changes .It appear be superior than CT in detecting bone marrow edema and early cartilaginous changes(63).Another advantage of MRI is that it doesn't include exposure to radiation.The presence of sacroiliitis in the imaging techniques (x-ray and MRI) in the presence of the clinical manifestations is substantially diagnostic for AS.Using of MRI in detecting the inflammation of the sacroiliac joint and the spine together with the new definition of inflammatory back pain(IBP) play an important role in earlydetection of SPA in the non-radiological stage.(65)

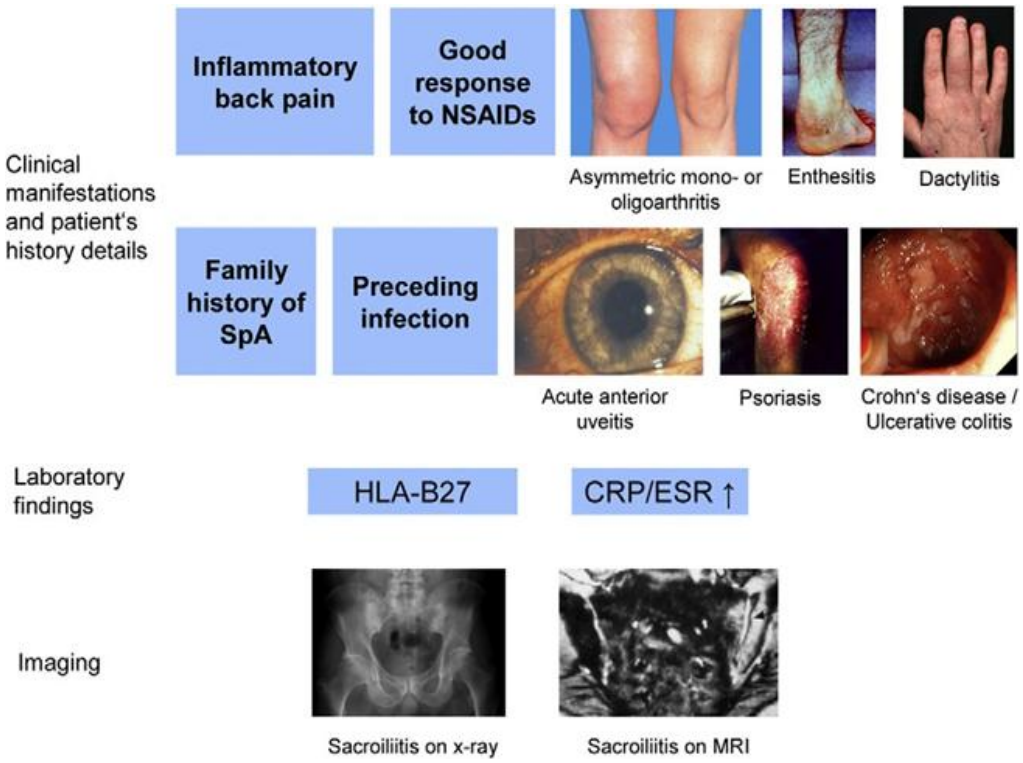

Figure 1clinical, laboratory and imaging manifestations of SPA

Clinical, laboratory and imaging manifestations of SpA, which are relevant for early diagnosis (5)

Current classification criteria:

-The ASAS classification criteria for axial SPA:

In the beginning of this century, the conception of axial SpA as a disease with two branches has been raised: with sacroiliac joints radiographic changes (ankylosing spondylitis [AS] or radiographic axial SpA) and without (non- radiographic axial SpA [nr-axSpA])(47,62) .With the presentation of recent and efficient options of treatment, like tumor necrosis factor (TNF) blockers,(66–68) it has become critical to detect the disease as soon as possible to give the patients a chance of treatment in the early course of the disease. As the usually used classification criteria, the modified New York (mNY) criteria for AS,(69) could not catch persons with early disease (i.e. sacroiliac joints without structural damage on X-rays) and proof of the capability of magnetic resonance imaging (MRI) to find active inflammation of sacroiliac joints and the spine in the beginning of the disease course (65,70,71), The new ASAS criteria was established .ASAS classification criteria have been suggested for axial SPA patients who suffered from chronic back pain and the onset is before the age of 45 (4).

The new ASAS classification criteria were advanced and published in 2009(72) They classify patients as having axial SpA even before occurring of structural damage in the sacroiliac joints. In accordance with new ASAS classification criteria,(72) at early stage of the disease this is probable either by using the 'clinical' arm, where the entity of HLA-B27 is compulsory with an supplementary two or more SpA features (Figure 1) or using the 'imaging' arm with signs of MRI active sacroilietis with at least one other SpA feature or.moreover, at a later stage classification is also probable when progressive chronic changes of the sacroiliac joints can be

seen in the traditional radiograph with reference to the mNY(69) and at least one other SpA feature is exist. These criteria demonstrated a specificity of 84.4% and a sensitivity of 82.9% , obviously exceeding the original European Spondyloarthropathy Study Group and Amor criteria.(69) concentrating on the so-called 'imaging arm' alone, the ASAS classification criteria showed a specificity of 97.5%. and a sensitivity of 66.2%.Furthermore,favorable results for sensitivity and specificity were presented, when these criteria were used to other cohorts and tested against the rheumatologist's diagnosis as the gold standard.

These were similar to the primary outcomes with a specificity between 62% and 95%.and a sensitivity between 68% and 87% At proceedings of the primary cohort (72), the positive predictive value that patients who first fulfilled the criteria would still be diagnosed with axial SpA was perfect with 93.3%. (73)within 3–5 years by the rheumatologist responsible for treatment .These classification criteria have been accompanied by some changes as a new definition of active MRI sacroiliitis (47) a new definition of inflammatory back pain,(74) and new classification criteria for peripheral SpA and SpA in general.(3)

-ASAS classification criteria for peripheral arthritis:

ASAS classification criteria have been also suggested for peripheral SPA(3).In accordance to these criteria in the presence of arthritis or enthesis's or dactylitis we are at a need of at least one of the major criteria which include psoriasis , HLA B27 ,inflammatory bowel disease ,uvietis, sacroiliitis (CT or MRI) or preceding infection or two or more of the following criteria(enthesitis ,arthritis, inflammatory back pain in the past,dactylitis and postive family history of SPA) .The specificity of this criteria is 82.9 % and sensitivity 77.8 % (3) (fig 2).

Diagnostic tests (there are no specific laboratory tests for AS):

There are no disease specific autoantibodies detected until now in contrast to rheumatoid arthritis and other connective tissue disease .However , there is a genetic marker(HLA B27) which is associated to the disease strongly about 80 % of patients with AS are HLA B27 positive(47) in contrast to about 8% in general white population(65). That makes this marker relevant as a diagnostic tool AS. it occurs only in a minority (about 5%)of HLA B27 positive persons in spite of this strong association between HLA B27 and AS(5) . Acute phase reactants like Erythrocyte sedimentation rate (ESR) and C-reactive protein plays a minor role in the diagnosis of early SPA because about 50 % of patients of SPA have normal values of thes tests.Now CRP becomes relevant to assessment of the disease as it denote active inflammation associated;while weakly, with the clinical parameters as pain in the spines ;and predict advancement in the sacroiliac joint and the spine(5).

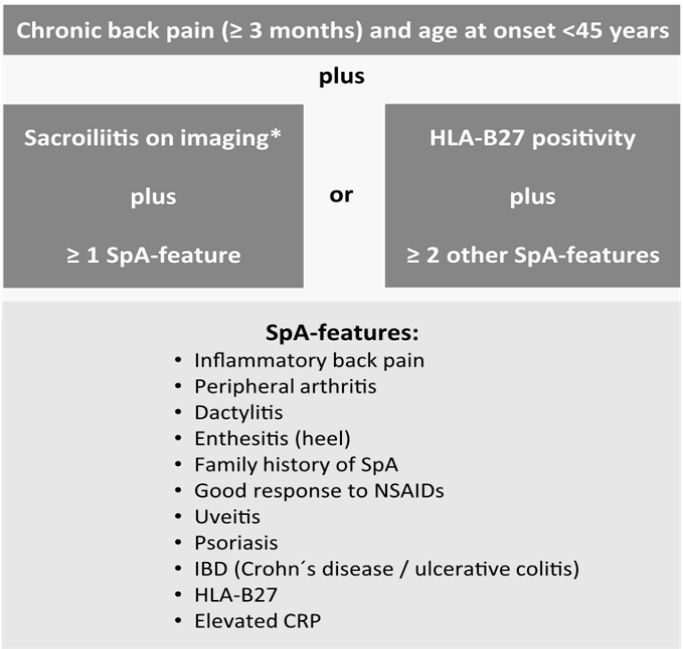

Figure 2 (ASAS) classification criteria for axial SPA

*Sacroiliitis on imaging refers to definite radiographic sacroiliitis according to the modified New York criteria or active sacroiliitis on magnetic resonance imaging according to the ASAS consensus definition.
CRP, C-reactive protein; HLA-B27, human leucocyte antigen-B27; IBD, inflammatory bowel disease; NSAIDs, nonsteroidal anti-inflammatory drug.

Final set of classification criteria for peripheral spondyloarthritis (SpA) (set 2D) selected by Assessment of SpondyloArthritis international Society (ASAS).

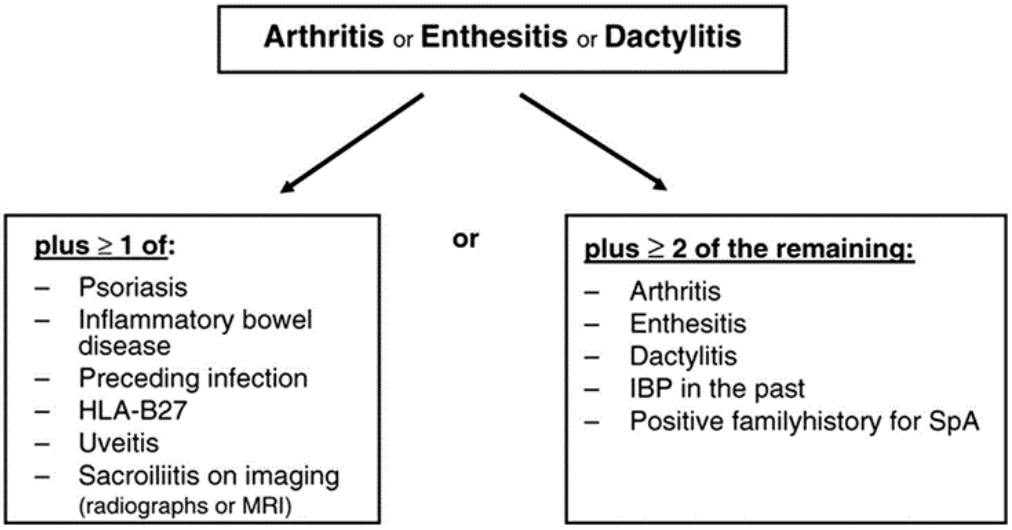

Figure 3 ASAS classification criteria for peripheral SPA

Assessment of Spondylarthrosis International Society (ASAS) classification criteria for axial and peripheral spondylarthritis.(3).

Treatment:

The main target of the treatment is to achieve remission with low activity of the disease as a secondary target. For axial spondyloarthropathy the radiological and the non-radiologicalfoms , remission was known as decrease the BASDAI score together with normal CRP value or decrease ASDAS (45)that contains the results of erythrocyte sedimentation rate or CRP.

The new recommendation of (ASAS and the European League Against Rheumatism for management of axial spondylarthritis from 201763) is the same withthe treatment recommendation (from the American College of Rheumatology/ Spondylitis

	Axial manifestations: back pain and stiffness	**Peripheral manifestations: arthritis, enthesitis, dactylitis**
First line therapy	**NSAIDs**	
	Non-pharmacological treatment: education, exercise, physical therapy, rehabilitation, patient associations, self help groups	
	Local steroids	
	csDMARDs (Sulfasalazine)	
Second line therapy	**bDMARDs: TNF α inhibitor or IL-17 inhibitor**	
	Analgesics	
	Surgery	

Association of America /SPARTAN from 201664

Table1: Lines of treatment of ankylosing spondylitis

Treatment algorithm for axial spondylarthritis (SpA) based on the Assessment in Spondylarthritis International Society/European League Against Rheumatism(43) and American College of Rheumatology/ Spondylitis Association of America/SpA Research and Treatment Network(75)recommendations.bDMARDs, biologic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; IL-17A, interleukin-17A; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor.

First line treatment:

The first line of treatment according to this recommendation involve two parts the non the pharmacological treatment by education of the patient about the nature of the disease , regular exercise and physiotherapy to improve the mobility as well as decreasing the deformity helping the patient to have a better quality of life and the use of non-steroidal anti-inflammatory drugs , involving cyclooxygenase-2 antagonists (selective -COX 2). , traditional DMARDs or glucocorticoids used in cases which show poor response to NSAIDs.)(43).

Not steroidal anti-inflammatory drugs:

Not steroidal anti-inflammatory drugs are very efficient with axial spondylarthritis patients by decreasing back pain and stiffness that's why it is recommended as the first option treatment for these patients.There is no variation in the efficiency of NSAIDs(76) .patients usually respond during the first 2 weeks of treatment with NSAIDs but in the responders during the first 24 weeks there is a much increase in the response rate(77) .The usage of NSAIDs should be according to patient symptoms .decreasing the dose or even discontinuation of the drug should be tested if there is a remission.It seems to show more effectiveness of the patients treated early ,obtaining a remission rate of about 35 % in patients who treated early in the course of the disease (<3 years of disease duration)(77)comparing to 12-15 % in patients with late disease.(78,79)The safety of using NSAIDs for long time is still a concern .As the data availableregarding long term using of this agents is limited for AS while it is more for rheumatoid arthritis and osteoarthritis(76).In two randomized controlled trials(80)(81) reported that there is no increase of NSAIDs side effects when used in AS therapy in comparison to placebo during 12 weeks. Irregular using of NSAIDs was linked with increase the mortality rate in a Norwegian cohort of patients with long standing AS(82).And also in apopulation based retrospective study(83) from canada using data of administrative health using of NSAIDs was also linked with decreasing the risk of cardiovascular diseases in this population.

Treatment with NSAIDs show a benefit as reducing inflammation and increasing mobility in patients with axial spondylarthritis, agents that may play arole in decreasing cardiovascular morbidity.Nevertheless, patients should be aware of the side effects of this agents that may result from long standing usage like cardiovascular , renal and gastrointestinal risks(76). A meta-analysis of randomized trials in patients using NSAIDs whatever the disease for at least 4 weeks , the potential risks of major cardiovascular adverse events were 1·37 for celecoxib and 1·41 for diclofenac, showing no variation between cyclooxygenase (COX)-2 selective and non-selective NSAIDs—but naproxen was excluded as it is not associated with increase(84)

Conventional disease modifying anti rheumatic drugs and glucocorticoids:

The disease modifying antirheumatic drugs (DMARDs) such as methotrexate,leflunomide or sulfasalazine are in general not effective in the treatment of axial manifestations of spondylarthritis while it may have aminor role in the treatment of peripheral manifestations when it occur together with the axial disease(2)There is an outstanding discussion regarding whether the combination of traditional DMARDs with biological drug may play a role in preventing the development of anti-drug antibodies (ADAs) toward the biological agents and thus increases the drug survival rate in these patients.while these advantage of combining DMARDs usually methotrexate with a TNF blocker was demonstrated in some investigations(85,86) of axial spondylarthritis patients but not in others.(87) Then such combination is not recommended that is in line with current treatment recommendation(43,75).Regarding systemic glucocorticoids , a high dose of about 50 mg or more per day is required to produce measurable treatment effects on the activity of the disease while it is not recommended to use it for a long period (88).

Second line treatment:

TNF inhibitors:

There are TNF inhibitors which is available for the treatment of ankylosing spondylitisin the the EC, USA, and other parts of the world infliximab, (66)etanercept,(68) adalimumab(67), golimumab,(89) and certolizumab (table).(90) .using any of these TNF blockers in the treatement leading to favorable results in the articular manifestations ,CRP levels and the detectable MRI sacroiliac inflammation. Etanercept is not efficient

in inflammatory bowel disease in contrast to monoclonal antibodies , that showed a favorable response in uveitis more than psoriasis(43,75).

TNF blockers except infliximab ,have already accepted to be effective for other clinical subsets of axial spondylarthritis the European Union (EU) and elsewhere depending on the results of phase 3 trials (90–93) while it is still not approved in USA .patients with objective signs of inflammation as positive CRP or active MRI in the sacroiliac joint or the spine are the only patients who get benefit from the EU label. The presence of this active signs not mandatory for the treatment of AS patients , although this patients who are positive for this indices usually respond better than thos who don't.(94)

For axial spondylarthritis patients,the best predictors of agood response to TNF blockers are raised CRP ,short symptom duration (or young age)(73) Usually discontinuation of TNF blockers in patients achieved a good response result in a relapse in 75-90 % of cases(95,96)whatever treatment with NSAIDs is continued or not (97)but if the dose of TNF blockers is reduced in good responders it will be tolerated in about 52-86% of patients (98)(99)

Other biological disease modifying antirheumatic drugs:

Other disease modifying anti rheumatic drugs like interleukin -1 receptor antagonist , abatacept a T-cell modulator and anakinra are tested in AS patients in small prospective studies showing no better effect than placebo.(43,75) A similar prospective open label trial was done on rituximab(100,101) a monoclonal antibody directed against CD 20 on B cells showed nonsignificant results.Tocilizumab(102) and sarilumab both are monoclonal antibodies directed against interleukin-6 receptor were tested also in two. placebo controlled double blinded studies showing no efficacy compared to placebo in anti TNF native patients.

In two phase 3 trials, secukinumab the anti-interleukin-17 inhibitor was efficient in AS patients and depending on this results now it have been approved in the EU , USA and elsewhere as a treatment of AS .The favorable response was maintained through 52 weeks of treatment in both studies.A dose of 300 mg secukinumab which is more effective than 150 mg in the treatment of psoriasis isnt approved yet for the treatment of AS,The reported effectiveness of secukinumab appear to be close to the response achieved by TNF blocker trials achieved in the same patient group. Secukinumab is also efficient in the subgroup of patients whom therapy with TNF blockers failed or discontinued to any reason(103).However , the role of Interleukin -17 inhibitors in the treatment of axial spondylarthritis needs more clinical experience. And also there is aneed of comparing the effectiveness of secukinumab treatment in patients failed to respond to a first TNF blocker with the effectiveness of using another TNF blocker. One prospective open-label trial(104) of ustekinumab (a monoclonal antibody against the p40 subunit of interleukin-12 and interleukin-23)seems to be effective in patients with ankylosing spondylitis. The oral Janus kinase inhibitor tofacitinib has been testedin AS patients in one phase 2 double-blind placebo-controlled dose-ranging study(105) showing promising results on clinical and MRI response that need confirmation in a large trial. oral PDE4 inhibitor Aprimlast was tested in AS patients a large placebo -controlled phase 2 trial with no superiority of it on placebo.

II. Conclusion

Ankylosing spondylitis patients vary in their clinical features and response to treatment. With adequate understanding to the nature of the disease,The patients could achieve a more favorable outcomes.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Lingli Dong. “Recent Insights in Ankylosing Spondylitis.” IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 05, 2019, pp 01-13.