A Review of Ankylosing Spondylitis

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Abstract

Ankylosing spondylitis (AS) is a systemic autoimmune disorder that induces ankylosis of the spine (fusion of the vertebrae at their various joints) and inflammatory arthritis of peripheral joints among other symptoms. Overexpression of cytokines, the presence of genetic mutations not exclusive to the human leucocyte antigen (HLA)-B27 region, and environmental factors all have large roles in the progressive development of AS. Although a definitive pathology continues to be sought after, researchers believe the adaptive immune system in AS patients attacks fibrocartilaginous entheses (supportive connective tissue between bone and attached structures like tendon, ligament, and fascia). AS markedly reduces proper systemic functioning in several areas of human physiology, including the musculoskeletal, cardiovascular, neurological, psychiatric, and reproductive systems in both genders. A diagnosis for this disease requires the presentation of several qualifying symptoms, namely chronic inflammatory back pain, peripheral joint arthritis, enthesitis (inflammation of the enthesis not associated with a joint), uveitis (inflammation of the uvea or inner eye layer), and positive response to non-steroidal anti-inflammatory drugs (NSAIDs), with radiological support through x-ray or magnetic resonance imaging (MRI). Upon an AS diagnosis, patients should engage in healthy lifestyle changes, non-impact exercise, and taking NSAIDs as the first pharmacological treatment. Symptoms unresolved by NSAIDs are then treated with disease modifying antirheumatic drugs (DMARDs) and/or biologic medications like a monoclonal TNFα antibody to prevent further disease progression. Continued research to understand the association between AS

and interleukin (IL)-17/IL-23 is needed for development of additional biologic

treatments.

A Review of Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a complex auto-immune disorder with a 0.5-0.9% global prevalence that affects males two to three times more often than female patients (Jamshidi et al., 2014; Sieper, Braun, Rudwaleit, Boonen, & Zink, 2002). Ankylosis of the vertebrae and surrounding connective tissues, especially within the sacroilial joints, leads to reduced mobility of the spine and rib cage. AS characteristically develops in early adulthood between the ages of 20 and 40 years-old and tends to worsen with age as the disease progresses (Calin, 1984). While a human leukocyte antigen (HLA)-B27 gene mutation often corresponds with an AS diagnosis, the etiology of the disease remains unknown. A distinctive pathogenesis is also unknown. The disease's correlation with HLA-B27, increased IgA antibody levels in mucus, and chronic inflammatory histology suggest AS develops from excessive immune mediated responses, but the exact mechanism of action is still to be determined (Westerveld, Verlaan, & Oner, 2009). This review serves as an additional resource to educate primary care physicians and others about the theorized pathology, physiology, and treatments associated with ankylosing spondylitis.

Pathology

Enthesitis is often considered a hallmark of AS, possibly the root condition leading to ankylosis. The condition refers to inflammation of an inserted structure of connective tissue onto a bone, such as a ligament, tendon, or sheath of fascia. Fibrocartilage of the bone at the enthesis site appears to be targeted by autoimmune responses in AS (Sieper et al., 2002). Bone marrow biopsies from AS patients (AS[+] bone

marrow) showed evidence of edema (swelling due to increased presence of fluid) with

elevated levels of Cluster of Differentiation 8+ (CD8+) cytotoxic T cells (kill infected or

cancerous self cells), CD3+ T cells, CD4+ helper T cells (activate innate immunity cells

like macrophages), and CD20+ B cells. These findings indicated an active immune

response occurred within sterile bone marrow of AS patients, meaning no exogenous

pathogens such as viral or bacterial infections initiated this auto-immune response. The

immune cells present appeared to actively break down enthesis fibrocartilage surrounding

vertebral facet joints with their associated ribs and neighboring vertebrae as well as the

entheses' articulating bone tissue, which was also comprised of fibrocartilage. Other

areas of noted damage included fibrocartilaginous entheses about peripheral joints, like

the hip and knee, and entheses along the shafts of long bones, such as the insertion of the

tibialis anterior muscle onto the tibia (bone that makes up the shin). Research of the

pathology of AS finds that inflammatory destruction not only affects the entheses of the

spine, but also damages the annulus fibrosus (fibrous exterior portion of the intervertebral

disc that connects one vertebral body to another via ligamentous structures seen in Figure

1) which fuses neighboring vertebral bodies over time (Sieper et al., 2002).
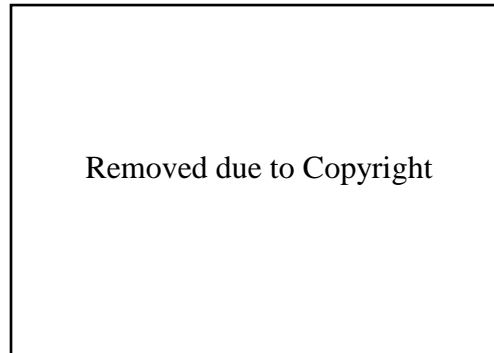
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Figure 1. Illustration of human spine with identified compartments of the intervertebral disc and the spinal cord (sourced from http://www.bionebio.com/startling-top-human-anatomy-and-physiology-of-the-spine-pictures/pulposus-anatomy-and-physiology-of-the-spine-spinal-cord-spinal-nerves-nucleus-intervertebral-disc-annulus-fibrosus-pinal-cord-is-located/ under Pulposus Anatomy and Physiology of the Spine).

Regarding the vertebral column, an influx of mononuclear immune cells directly correlates with osteitis (inflammation of the bone) and edema within AS[+] bone marrow, thus indicating an autoimmune response on the non-infected bone marrow. T cells most likely initiate a response after activation by a self-antigen of cartilaginous descent to ultimately induce the lysis of cartilaginous support cells through an inflammatory immune response. This lysis damages healthy cartilaginous tissue to form an ankylosed or "bamboo" spine, seen in Figure 2. This outcome is classic for an AS patient after ossification occurs (Sieper et al., 2002).

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Figure 2. Radiographic image of an ankylosed spine, also known as "bamboo spine." The arrows indicate marginal osteophytes, ossified outgrowths of the degenerated cartilage between vertebral joints shown. (Image sourced from Dr. Donald Corenman of the Steadman Clinic.)

Within Jethwa and Bowness's 2016 research, three mechanisms of AS spinal tissue degradation were postulated regarding the vague relationship between the class I major histocompatibility complex (MHC) molecule HLA-B27 and the CD8+ T cells associated with fibrocartilage. The exact role of the HLA-B27 in AS remains unknown, yet three theories of inflammatory function are currently held. HLA-B27, present on all nucleated somatic cells, functions as a membrane surface protein that induces a protective lysis response against identified foreign pathogens (Jethwa & Bowness, 2016). This occurs after HLA-B27 presents an intracellularly processed antigenic peptide to a CD8+ T cell to initiate an immune response toward the infective agents. The first theory of HLA-B27 involvement in AS focuses on the proposed cross-reactivity between HLA-B27 and host cell membrane peptides that occasionally occurs. For unknown reasons, HLA-B27's inability to recognize certain host cells as "self" induces an immune response on these cells of the host tissue rather than the invading microorganisms themselves, thus

giving rise to an auto-immune pathology. When HLA-B27 reacts to self-antigens in this

dysfunctional manner, the peptide can be classified as arthritogenic as it initiates an

undue inflammatory response. The second theory states that genetically mutated HLA

surface peptides induce an intracellular inflammatory response within its leukocyte's

endoplasmic reticulum (ER) (the organelle in which protein synthesis and folding

occurs). The final theory suggests that the innate immune system targets misfolded HLA

proteins and destroys them through an inflammatory response (Jethwa & Bowness,

2016). Leukocyte presentation of mutated HLA-B27 in AS may induce their own

destruction as immune cells, particularly natural killer (NK) cells, target the HLA-B27

homodimer with the killer cell immunoglobulin-like receptor 3DL2 (KIR3DL2); Chan et

al. found that patients with spondyloarthritic and enthesistis-related arthritic diseases

have elevated expression of CD41+ T cells and the KIR3DL2 receptor on NK cells

(Chan, Kollnberger, Wedderburn, & Bowness, 2005). Localized inflammation upon

HLA-B27 homodimer and KIR3DL2-containing cell binding occurs through the T helper

cell production of interleukin 17 (IL-17; a pro-inflammatory cytokine induced by IL-23).

Increased numbers of these KIR3DL2 associated cells and a raised concentration of IL-17

were collected from the synovial fluid of spondyloarthritic patients while in AS

specifically, a raised number of IL-17 associated immune cells were isolated from the

spinal facet joints (Appel et al., 2011).

Research conducted with identical twins concludes this relationship between AS

and HLA-B27 cannot be the only cause of AS; other genes outside the HLA coding

region can be collectively responsible for disease development. Nearly 5-10% of patients

diagnosed with AS are HLA-B27 negative, which suggests that multiple mutations

collectively cause the disease. As of 2016, Ellinghaus et al. presented AS as genetically

linked to Crohn's disease (CD), primary sclerosing cholangitis (PSC), psoriasis (PS), and

ulcerative colitis (UC) and thus expresses a high rate of comorbidity with these other

autoimmune diseases. Ellinghaus et al. concluded the significant association of AS and

these disorders are due to pleiotropy (one gene or gene affecting multiple phenotypic

conditions), supported by their finding of 166 related, genome-spanning loci not

associated with major histocompatibility complex (MHC) gene regions (Ellinghaus et al.,

2016). These AS related loci were determined to mainly affect natural killer (NK) cells,

CD34+ bone marrow cells, and undifferentiated immune cells by altering regulatory

immune response pathways and the hematopoietic system. Typical T cells found in AS

patients tend to secrete abnormally lower levels of tumor necrosis factor α (TNFα), a pro-

inflammatory cytokine used to signal the destruction of pathogens and tumor cells by

immune cells, and IL-10, a regulatory cytokine that facilitates the extent of an immune

response by managing the concentrations of several pro-inflammatory cytokines (Sieper

et al., 2002). A deficiency in these particular cytokines often prevents effective innate

inflammatory responses against viral and bacterial pathogens which leads to either serial

or chronic infections. With continued exposure to these viral or bacterial antigens, the

risk of cross-reactivity between adaptive immune cells and continuously infected tissue

increases greatly and may lead to development of autoimmune diseases (Sieper et al.,

2002). Other such environmental factors like an altered microbiome within the gut and

exposure to certain toxins or drugs can also collectively lead to the pathogenesis of AS

(Jethwa & Bowness, 2016). Overall genetically, AS appears to require multiple gene

mutations for an active disease state with HLA-B27 taking about 30% of the genetic

threat. Mutations within the respective genes that code for endoplasmic reticulum

aminopeptidase 1 (ERAP1) (an ER enzyme that packages peptides, including HLA-B27,

for surface presentation), the IL-23 receptor (IL-23R), and other genes associated with

the IL-17/IL-23 pathway follow HLA-B27 in prevalence (Jethwa & Bowness, 2016).

        The most recent pathological research conducted in regard to autoinflammatory

diseases like AS focuses on the IL-17/IL-23 pathway. T helper 17 (Th17) cells stem from

the regulatory branch of the helper T cell family and are notable for their IL-17

production and maintenance of mucosal barrier integrity through pathogen destruction.

Decreased or mutated Th17 populations have been connected to chronic inflammatory

states, dysregulation of healthy gut microbiomes that allow pathogenic colonization, and

often autoimmunity (Hartigan-O'Connor, Hirao, McCune, & Dandekar, 2011). Sherlock

et al.'s 2012 research involving murine models indicated that extrinsically introduced IL-

23 to healthy mice facilitated the development of symptoms associated with

spondyloarthritis. This phenotype occurred through IL-23 action toward various T cells

receptors, namely IL-23R which induced a fairly instantaneous inflammatory response in

local enthesis tissue without additional immune involvement, and caused increased

production of pro-inflammatory cytokines, especially IL-17, along with other chemokines

for later innate and adaptive immune responses (Sherlock et al., 2012). Autoinflammatory

responses within the enthesis were assumed to be mediated by IL-17 associated immune

cells without regulatory capability because Th17 cells were not isolated from localized

enthesis inflammation (Appel et al., 2011). Increased concentrations of IL-23 producing

cells, as well as elevated IL-17 and IL-23 serum concentrations, have been isolated from

AS+ subchondral bone marrow and synovial fluid when compared to healthy patients

(Davidson et al., 2011). More research regarding IL-23's mediation of Th17 cytokines

and their subsequent inflammatory response should be conducted to further clarify the

pathway depicted in Figure 3 and better understand its association with AS pathology.

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Figure 3. Extended pathway of interleukin (IL)-17 and IL-23 (Jethwa & Bowness, 2016).

Physiology

Cardiovascular Physiology

AS manifests itself in different ways over the course of a patient's life, affecting

the cardiovascular (CV), musculoskeletal, and neurological systems in detrimental ways.

Certain serum protein levels are quite abnormal for AS patients. Increased levels of

fibrinogen (a glycoprotein that aids in blood clot formation), IL-6 (a pro-inflammatory

cytokine), and C-reactive protein (CRP; a protein used to indicate levels of inflammation

in the body as it binds to phospholipids of damaged cells to initiate the innate immune

system response through the complement pathway) raise the viscosity of blood, which

increases its likelihood to clot and mount a defense against self-antigens throughout the

spine, entheses, peripheral joints, and other AS manifestation areas. These higher protein

concentrations raise the erythrocyte sedimentation rate (ESR) which also increases the

viscosity of the blood. AS patients are more likely to suffer from strokes and myocardial

infarctions (MI) since blood clots form more readily and the arteries tend to be coated

with fatty plaques. For unknown reasons, AS patients present with decreased levels of

triglycerides and total body cholesterol, especially high density lipoproteins (HDLs)

which regulate plaque formation in the arteries. This decrease in HDL leads to a greater

prevalence of atherosclerosis in AS patients; these patients are twice as likely to

experience strokes and MIs compared to healthy individuals (Park et al., 2012).

  As the disease progresses, AS patients undergo an abnormal thickening of their

mitral and aortic valves as marks of high blood pressure and continual systematic

inflammation. Along with thickening of the heart valves, the thickening of the intima-

media (innermost layer of an artery wall), especially within the carotid arteries, increases

significantly with age (Mathieu, Gossec, Dougados, & Soubrier, 2011). These heart valve

changes most likely occur after disease onset without noticeable effects to the patient

(Park et al., 2012). Usten et al. measured left ventricular systolic function in AS patients

with highly sensitive speckle tracking echocardiography (STE) rather than the commonly

used conventional and Doppler echocardiography (ECG) techniques. Both the

conventional and Doppler ECG machines are incapable of detecting minor ventricular

dysfunctions (Ustun et al., 2015). The use of STE quantified significantly lower left

ventricular systolic and diastolic strain measurements with all STE parameters in AS

patients compared to controls. These findings indicated weakened overall function of the

left ventricle possibly due to systemic inflammation that damages cardiomyocytes

(muscle cells of the heart) over the course of the disease.

Musculoskeletal Physiology

As previously discussed, AS mainly debilitates the skeletal system at its

cartilaginous sites like the spinal joints (articulating its superior and inferior vertebra and

lateral ribs), the peripheral joints, and the entheses throughout the spine and other

individually symptomatic areas. Activated immune cells targeting AS-associated self-

antigens break down cartilaginous fibers of joints and entheses until the damaged tissues

begin to ossify, producing new bone tissue in the place of flexible attachment sites for

tendons, ligaments, and fascia. Ossified joints and entheses result in decreased mobility.

Original flexibility diminishes, reducing physical strength and increasing AS-associated

back and joint pain particularly during sedentary periods. As stated earlier, complete

fusion of vertebral bones may occur in the axial spine when the outer linings of the

intervertebral disks begin to ossify, creating what is known as "bamboo spine." Fused

spines like this fracture easily under trivial traumas, like bumping into a stranger, and

heal poorly; they lack stability and durability as the disease progresses and greatly

increase neurological complications during serious traumas involving the cervical spine

(Westerveld et al., 2009). A prematurely stiff or nearly fused spine also constricts

expansion of the rib cage which restricts airflow into the lungs below a normal level

(McBride, King, Baikie, Crean, & Sircus, 1963). A constricted rib cage raises stress on

the pulmonary and CV systems, leading to reduced oxygen intake and increased heart rate that accounts for the structural changes in the heart and arteries.

Neurological Physiology

       The autoinflammatory nature of AS alters proper function of both the central nervous system (CNS; neurons associated with the brain and spinal cord) and the peripheral nervous system (PNS; neurons outside the CNS). The hypothalamic-pituitary-adrenal (HPA) axis is comprised of three separate endocrine organs that together regulate and counteract stress, immune responses, emotions, and metabolic expenditure. When tested in AS patients via the standard insulin tolerance test (ITT), the HPA axis will present normally when compared to control subjects, unlike similar rheumatic diseases like rheumatoid arthritis (RA) (Kirnap et al., 2008). A statistically insignificant, mild decrease in adrenal function was noted in tested AS subjects based on their abnormally lower basal cortisol levels prior to ITT testing. These results were possibly attributed to patients' previous NSAID treatments or how increased levels of pro-inflammatory cytokines, mainly IL-1, IL-6, and TNFα, appeared to raise adrenocorticotropic hormone (ACTH) levels through modifying the effects of corticotrophin-releasing factor (Imrich et al., 2004). Further dynamic testing indicated no significant adrenal malfunction was present with AS patients (Kirnap et al., 2008).

       Although the hypothalamus and pituitary gland appear unchanged within the AS brain, other networks of the brain involving attention, executive control, and somato-sensory function restructure with the course of the disease and communicate poorly. Significant reported fatigue in AS patients was inversely correlated with quantified spinal

mobility and emotional stamina; gray matter (neuronal bodies of the CNS associated with sensory perception, emotions, and decision-making capabilities) within the attention networks, somatosensory cortices (areas of the cerebrum that facilitate thoughts and perceptions into physical actions), and caudate nucleus (segment of brain that assists regulating goal-directed actions, memory, learning, and attention stabilization) were also negatively correlated with fatigue scores (Wu, Inman, & Davis, 2014). This indicates that AS patients experiencing an active disease state often have difficulty processing external stimuli appropriately and accomplishing higher cognitive goals. AS patients also tend to endure continuous neuropathic pain (perceived pain associated with malfunctioning of the somatosensory nervous system rather than damaged tissue) in which atrophy of gray matter in the aforementioned brain regions generally leads to poor control of the limbic system (midbrain regulator of emotions) and pain modulating centers (Wu, Inman, & Davis, 2013). AS neuropathic pain usually involves "shooting" or "stabbing" pain in individual problem areas along with dull, achy soreness associated back pain stemming from inflammation surrounding spinal nerves.

Diagnosis

Historically, the concept and manifestations of AS were poorly understood by physicians until the mid-1900s. The first AS-focused studies associated the disease with other forms of inflammatory arthritic diseases like psoriatic arthritis, rheumatoid arthritis, Reiter's disease, and inflammatory bowel disease (Sieper et al., 2002). By 1991, the clinical grouping of the aforementioned spondylarthropathies (SpAs) was modified by the European Spondylarthropathy Study Group (ESSG) to allow for more distinctive

diagnoses between the diseases (Dougados et al., 1991). All these auto-immune disorders

share common symptoms like arthritic joint pain, stiffness, and the like although their

immunological mechanisms are not identical because they often require different

treatments. A proper ankylosing spondylitis diagnosis requires a patient to fall within a

younger adult age set and present with a specific combination of symptoms within a

designated time constraint for the onset of severe symptoms. These AS diagnosis

qualifications were detailed in the *New York Criteria for Ankylosing Spondylitis*

published in 1973 and act as the current standardized basis for scientists diagnosing

research participants before undergoing any AS studies.

In the early 1960s, the minimum requirements for an AS diagnosis were "bilateral

loss of definition or irregularity of the sacro-ilial spaces with subchondral sclerosis"

(McBride et al., 1963). No discussion of the ankylosis of the cervical spine or accessory

symptoms (like the now hallmark uveitis and enthesitis) occurred, which left this

diagnostic system incomplete and unable to differentiate between multiple SpAs. A more

complete evaluation of AS symptoms was compiled in the original 1973 New York

Criteria diagnostic list as follows: 1) low back pain and stiffness lasting more than 3

months that is not alleviated by rest, 2) pain and stiffness in the thoracic region, 3) limited

motion of the lumbar spine, 4) limited chest expansion, 5) history of iritis or its sequelae,

and 6) x-rays showing bilateral sacroilial changes characteristic with ankylosing

spondylitis (excluding bilateral osteoarthrosis of the sacroilial joints) (Moll & Wright,

1973). Over the years, the need for a more comprehensive diagnostic system grew with

the collection of additional pathological and physiological information about AS;

multiple researchers then modified the New York criteria to include extra differential

symptoms and characteristics of the current patient population seen in Table 1. Calin et

al. made additional requirements of "AS onset before age 40" and the "onset of disease is

insidious in nature" to better match the data of his sample and review populations (Calin,

Porta, Fries, & Schurman, 1977).

Table 1. *Modified Criteria for Ankylosing Spondylitis (Sieper et al., 2002).*

Radiologic criterion
Sacroiliitis, grade ≥II bilaterally or grade III to IV unilaterally
Clinical criteria
Low back pain and stiffness for more than 3 months that improves with exercise that is not relieved by rest
Limitation of motion of the lumbar spine in both the sagittal and frontal planes
Limitation of chest expansion relative to normal values correlated for age and sex

Note: *The condition is definitely AS* if the radiological criterion is associated with *at least 1* clinical criterion.

Physicians analyze a patient's symptoms with the previously mentioned criteria in

mind to monitor alignment of symptoms with an AS diagnosis using a diagnostic
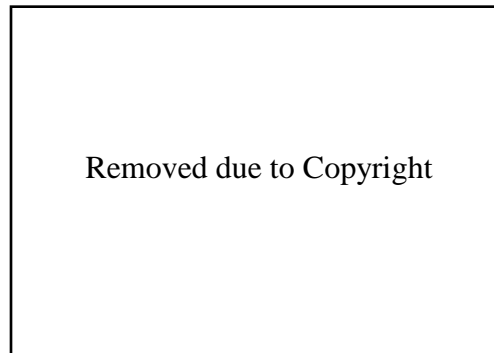
algorithm, seen in Figure 3.

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Figure 3. Diagnostic algorithm for axial SpA (early AS) starting with the assessment of inflammatory back pain (Sieper et al., 2002).

Confirmed symptoms farther down the pyramid of Figure 1 carry more diagnostic weight than those near the top due to the narrowly direct association with the disease. Accessory symptoms to inflammatory arthritis of the axial skeleton include enthesitis (inflammation of the enthesis that joins bone to collagen fibers of tendons, ligaments, and fascias), uveitis (inflammation of ovea, the middle layer of the eye), asymmetric arthritis of the peripheral joints, family history of the disease, a confirmed HLA-B27 gene mutation, raised C-reactive protein levels in the blood (CRP), and a positive response to NSAIDs. At least two of these accessory symptoms must be present in addition to spondylitis and radiographic evidence of sacroiliitis for an AS diagnosis to be made. A positive HLA-B27 genetic test is one of the strongest indicators of active AS. 90-95% of those diagnosed with the disease also have a mutation within an HLA-B27 coding region (Sieper et al., 2002).

Upon diagnosis, physicians have often incorporated the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) as a functional scale to measure the severity of a patient's disease and provide quantitative data regarding the efficacy of a newly applied treatment. The BASDAI reliably compiles a scaling of six major AS complaints: 1) fatigue severity; 2) pain in spinal joints; 3) swelling and pain in peripheral joints; 4) enthesitis severity (worded as "localized tenderness"); 5) duration of morning stiffness; and 6) severity of morning stiffness (Li et al., 2016). Patients can quickly record their personal evaluation of each symptom with a 1-10 scale (1 indicating no issue and 10 indicating the severest issue) in which each of the first four symptoms are given equal weight with the averaged morning stiffness symptom scales. This creates a 0-50 scale that is then divided by 5 for an official 0-10 BASDAI score used to rank and compare total AS severity among patients (Chung, Lau, Wu, Wong, & Mok, 2011). A BASDAI score of 4 or greater indicates poor disease management; these patients are prime candidates for altering their present treatment, possibly to include a biologic medication like a TNFα antibody. Clinical researchers use the BASDAI to identify appropriate candidates for new drug trials geared toward slowing AS progression and measure the success of the treatment. Aside from the BASDAI, other disease scoring tests specifically for AS are commonly used, such as Bath Ankylosing Spondylitis Metrology Index (BASMI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS), though the BASDAI is considered the "gold standard" for AS disease scoring (Zochling, 2011).

Treatments

Prior Treatments

The advancements in treating AS have become safer, more comprehensive, and more effective since the early 1900s. Before the 1950s, physicians attempted to treat AS symptoms with several rounds of x-ray therapy over the course of several months. The theorized goal of this therapy was to stimulate hormones that were presumably unbalanced to induce mast cells release of their higher concentration of sulfur. At the time, researchers believed mast cells, as well as other leukocytes, carrying more sulfur than usual absorbed it from cartilaginous fibers surrounding the sacroilial joints, thus damaging the cartilage which would then heal as bone tissue: the proposed etiological origin of AS (Tegner, 1946). A more involved understanding of the immune system as a whole and its specific relationship with AS proved this prior theory false. Although x-ray therapy relieved pain in treated patients, this now controversial treatment plays no role in preventing disease development today. No changes in bone sedimentation of inflamed joints or radiographic evidence of spinal damage were noted during the course of x-ray therapy, so the treatment was deemed ineffective in controlling the progression of AS. Even though the continual exposure to x-rays decreased a patient's pain, the treatment was discontinued throughout the United States when further research indicated that increased rates of cancer in AS patients stemmed from the carcinogenic therapy.

Non-pharmacological Treatment

One treatment doctors have reached a consensus on is the incorporation of physical activity into the daily lives of AS patients. Research finds that individuals with

AS who held a consistent exercise program over 4 months increased the function of their spine and peripheral joints significantly compared to sedentary AS patients (Zochling, van der Heijde, Dougados, & Braun, 2006). This study conducted by Zochling et al. (2006) compared the exercises prescribed and supervised by a licensed physical therapist to patient organized daily movement at home to see if one particular regime decreased AS stiffness and pain more than the other. Zochling et al. concluded that neither regime was more effective than the other; simply moving the joints and raising the heart rate consistently alleviates much of the symptomatic stiffness. They also found that while exercise decreased the patients' overall stiffness, their subjective levels of pain remained relatively the same as before exercise. Impact exercises, such as running and contact sports, are high risk activities for patients with active AS. Jarring movements associated with these exercises cause additional stress on the joints and spine an AS patient is unable to heal properly since damaged fibrocartilage is mistakenly converted into bone tissue, increasing the risk that injury could hasten the rate of disease progression (Zochling et al., 2006). Impact sports could potentially fracture a delicate, ankylosed spine which may not heal to regain functionality. Non-impact physical activities like bike riding, swimming, yoga, and gentle power walking are highly recommended exercise alternatives for AS patients.

Other recommended non-pharmacological lifestyle changes for AS include educating patients concerning their disease, its treatments, and daily restrictions; drinking alcoholic beverages in moderation; avoiding smoking and using recreational drugs; remaining hydrated throughout the day; eating a diet low in starches and sugars, possibly

adhering to a gluten-free and sugar-conscious diet, to avoid disease flare ups; and

committing to an appropriate sleeping regimen that includes at least 7 hours of sleep per

night (Zochling et al., 2006). Since an abnormal sleep schedule may further aggravate the

chronic inflammatory state, patients are recommended to adopt consistent sleeping habits

as newer research correlates adequate sleep with possible disease remission (Leverment,

Clarke, Wadeley, & Sengupta, 2017). The maintenance of mental health is also especially

important. Emotional stress left unchecked in an AS patient has the potential to increase

the diagnosis of depressive and anxiety disorders, along with a heightened level of

disease related pain. In a state of depression and anxiety, patients may be mentally unable

to complete their treatment of AS by remaining isolated and sedentary within their

homes, possibly avoiding exercise, increasing or decreasing eating, sleeping too much or

too little, and taking their medications in ways other than as prescribed. Patients

experiencing symptoms of depression along with their AS diagnosis should seek help

from a medical professional, either their general care doctors or a psychiatrist, and a

licensed counselor to discover the cause of these psychological concerns (Basler &

Rehfisch, 1991).

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

        NSAIDs are considered the cornerstone of AS therapy; NSAIDs are the cheapest

and longest studied drugs used to treat ankylosing spondylitis. These drugs exhibit

analgesic (relief from pain) and antipyretic (reduction of fever) properties by inhibiting

cyclooxygenase 1 and 2 (COX-1 and COX-2), enzymes that assist in antibody synthesis

and catalyze prostaglandins that regulate several physiological responses during local and

systemic inflammation (Bancos, Bernard, Topham, & Phipps, 2009). NSAIDs also

clinically modify multiple other branches of the innate and adaptive immune system

through the reduction of T lymphocyte activation and proliferation, monocyte activation,

cytokine production, and formation of leukotrienes.

Diclofenac, the most prescribed NSAID for AS, has been found effective and safe

in treating AS in long-term cases and short-term flare ups (Calabro, 1986). Typically,

75mg of diclofenac twice daily is enough to provide a therapeutic effect to treat

predominantly axial manifestations of the disease as well as peripheral joint arthritis and

enthesitis. Though the half-life of diclofenac lasts about an hour or two, the drug

continues to work actively in synovial fluid for up to 11 hours (Small, 1989). 200mg

daily of celecoxib, another commonly prescribed NSAID for AS patients, has the same

efficacy of treatment as diclofenac with fewer adverse gastrointestinal side effects (Sieper

et al., 2008). The mechanism of action for NSAIDs indirectly weakens the epithelium of

the stomach by the reduction of prostaglandin production, leading to the main adverse

effect of NSAIDs: stomach ulcers and increased sensitivity to gastric acid corrosion.

Since NSAIDs have long been the premier treatment of AS, a patient must undergo two

failed NSAID trials before a presiding rheumatologist considers alternative treatments to

include tumor necrosis factor-α (TNFα) blockers, discussed later in this review.

Disease-modifying Antirheumatic Drugs (DMARDs)

Low doses of DMARDs are also considered safe, first action drugs for AS. Anti-

malarial drugs, gold salts, various immunosuppressants, and methotrexate can be

incorporated into auto-immune disease treatment in general, with methotrexate as the

chief drug of the list to treat AS. Overall, normal AS patients tolerate DMARDs well with few serious side effects. (Pregnant patients should avoid methotrexate since the drug acts as an abortifacient; patients fighting an infection should avoid penicillins because the two drugs combined can lead to a fatal reaction.) Methotrexate's method of action inhibits the metabolism of folic acid, then inhibiting the activation of T cells by suppressing the intercellular adhesion molecules between T cells, causing B cells to selectively down-regulate, and inhibiting interleukin 1 ß cell surface receptors to effectively decrease the immune responses capable of damaging an AS patient's joints and entheses (Chen, Veras, Liu, & Lin, 2013). Research finds that a 12.5mg intramuscular injection of methotrexate once-weekly is effective to treat morning stiffness, disease intensity, and axial and peripheral joint functionality in older AS patients and patients in a later disease state. The state of disease progression can be physically viewed through radiographic imaging of the sacroilial joints as well as recording the range of mobility in affected joints using a goniometer. Methotrexate is often synergistically paired with infliximab, a TNFα blocker, to treat cases of AS ineffectively reduced by NSAIDs use. Methotrexate and other DMARDs should not be paired with NSAIDs; the combination of the drugs could cause a potentially fatal reaction (Chen et al., 2013).

Monoclonal TNFα Antibodies

TNFα is presumed to be a pivotal cytokine in AS pathogenesis; TNFα and other cytokines in its cascade pathway can be consistently collected from the synovial fluid, serum, and sacroilial joints of patients in an active disease state (Gorman, Sack, & Davis,

2002). Anti-TNFα drugs, usually a monoclonal human antibody, have proven some of the most effective drugs at treating spinal structures and peripheral entheses and preventing disease progression, which can be viewed via radiographic evidence. Extended treatment with anti-TNFα antibodies induces an immunosuppressive state in which the patient is more susceptible to illnesses like tuberculosis, influenza, and certain types of cancers, but many physicians believe the benefits of the drug sharply outweigh the risks of further illness. Three anti-TNFα agents are currently approved for use in the US and the UK: infliximab, etanercept, and adalimumab which are sold under the trade names Remicade, Enbrel, and Humira, respectively. Normally paired with a methotrexate drug, infliximab is a monoclonal antibody that binds up TNFα and is infused intravenously over 1-2 hours every 8 weeks (Braun et al., 2003). Etanercept is a small molecule that competes for the TNF-α receptor on cell surfaces, administered to patients in 25mg increments via subcutaneous injection twice weekly (Braun et al., 2003). The last anti-TNFα drug, adalimumab, is a 40mg portion of a monoclonal human anti-TNFα antibody injected subcutaneously biweekly. Even from the limited studies concerning the newly developed technology, researchers have concluded that these three anti-TNFα drugs, especially adalimumab, possess an extremely high efficacy in treating AS.

Since these drugs were only recently developed, long term effects on organs and their systems are currently unknown and the cost of production remains extremely expensive, with the retail price costing upwards of $1000 US per injection. Anti-TNFα antibodies have also been linked to new cancer diagnoses, especially lymphomas, following continued drug administration. Doctors and insurance companies try to reserve

these costly medicines for those with the most severe cases of AS that cannot be

controlled through other methods. Requirements for a TNFα blocker prescription include

1) a diagnosis of AS according to the New York criteria previously described (including

radiographic evidence of sacroiliitis); 2) failure of at least 2 adequate trials of NSAID

therapy; 3) persistence and worsening of disease activity; 4) threat of severe damage from

disease; and 5) likelihood of response to a TNFα blocker as determined by the

rheumatologist. Once a patient's conditions expresses these five conditions, a presiding

doctor can then prescribe one of the three drugs. If patients become actively diagnosed

with certain autoimmune disorders, infection, malignancy, or becomes pregnant, they are

disqualified from receiving TNFα blockers. Due to the potential cancerous side effects,

high cost, and high efficacy of the TNFα blocker drugs, doctors recommend infliximab,

etanercept, and adalimumab be taken in 6-12-week intervals after which the monitoring

physician assesses the level of disease improvement. If less than 50% relative

improvement occurs during the 6-12-week time period, the patient continues taking the

drug through the next period. If a patient experiences a relative improvement greater than

50%, the drug is discontinued during the next 6-12 week interval until the patient begins

to deteriorate again (Braun et al., 2003).

Proposed Therapies

Currently, no other biologic treatments specifically approved for AS are available

to patients beside TNFα blockers. New, promising research involving the treatment of

plaque psoriasis, a dermatological autoimmune disease genetically linked to AS, with

biologic drugs ixekizumab, secukinumab, and ustekinumab (respective trade names:

Taltz, Cosentyx, and Stelara; respective market release: 2016, 2015, and 2013) could lead to possible treatments for AS (Ellinghaus et al., 2016). Ixekizumab and secukinumab are both monoclonal antibodies that target IL-17 cytokines within the IL-23-T helper 17 pathway. According to Gomez-Garcia et al. (2016), both drugs were found more efficacious in treating plaque psoriasis in Japanese patients than TNFα monoclonal antibodies in short-term therapy yet both were more likely to lead to drug complications: infliximab use increased the risk for adverse effects (AE) other than infections while secukinumab increased patients' susceptibility to infection (Gomez-Garcia et al., 2016). Ustekinumab, a monoclonal antibody that binds to the shared protein subunit between IL-12 and IL-23, also exhibited significant efficacy in treating plaque psoriasis in the aforementioned study. Ustekinumab presented as the highest ranked efficacy-safety profiled drug tested by Gomez-Garcia et al. (2016), including ixekizumab, secukinumab, and popular TNFα antibodies, namely etanercept and adalimumab (Gomez-Garcia et al., 2016). Brodalumab is a monoclonal antibody not yet approved by the Food and Drug Administration (FDA) that functions as a competitive inhibitor for the IL-17A receptor that showed promise in treating plaque psoriasis effectively (Nakagawa, Niiro, Ootaki, & Japanese brodalumab study, 2016). These biologic drugs that prove effective in treating psoriatic patients should be further investigated especially in regard to possible treatment of AS. Preliminary research to understand the IL-23/IL-17 pathway in AS pathogenesis is currently underway in hopes of leading to clinical trials involving the aforementioned drugs (Jethwa & Bowness, 2016).

Ankylosing spondylitis is an auto-inflammatory disorder that targets cellular

surface molecules associated with fibrocartilage within entheses throughout the body,

mainly within the axial spine, resulting in reduced patient mobility and quality of life.

Cross-reactive immune cells, often expressing an allotype of HLA-B27 with the

abnormal ability to present self-antigens, illicit damage at these fibrocartilaginous sites

before the tissue heals as bone. Extensive deposition of bone in these tissues may produce

the "bamboo spine" characteristic to AS. Since the aforementioned cross-reactive

immune cells have constant access to their fibrocartilaginous auto-antigens, the body

experiences a state of chronic inflammation perpetuated in part by the IL-17/IL-23

cytokine pathway. Adverse cardiovascular and neurological effects associated with AS

stem from generalized chronically activated immune and chronic pain states,

respectively, while the musculoskeletal effects are more exclusive to the specific disease.

Proper diagnosis requires simultaneous presentation of multiple symptoms including, but

not limited to, insidious onset of back pain and stiffness lasting more than 3 months,

limited expansion of the ribcage, a positive response to NSAIDs, a positive test for HLA-

B27 mutation, peripheral arthritis, uveitis, enthesitis, and radiologic evidence of

sacroiliitis. Upon diagnosis, several courses of treatment exist for AS patients ranging

from healthy lifestyle changes to immunosuppressant antibody drugs. General

practitioners and rheumatologists recommend their AS patients avoid high-impact

exercise, smoking, the consumption of alcoholic beverages, gluten-based food products,

and irregular sleeping habits. Patients are encouraged to educate themselves regarding

their disease limitations in addition to preserving their mental health and partaking in

core-strengthening exercises. More severe cases of AS often require pharmaceutical

intervention with a combination of NSAIDs, DMARDs, and anti-TNFα antibodies, all of

which should depress the overactive immune system response for symptom relief and

slow disease progression. Each class of drug has its own list of benefits and drawbacks

that should be considered in totality prior to creating a patient's treatment plan.

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