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The latest advancements in the treatment of Ankylosing Spondylitis, considering gender, genetics, environment, and immunity: an insightful review

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ABSTRACT

Ankylosing Spondylitis (AS) is a type of arthritis that causes inflammation in various parts of the body, primarily affecting the spine. It is also known as Bechterew's disease, Bekhterev's disease, Morbus Bechterew, Bekhterev–Strümpell–Marie disease, and Marie's disease. AS can cause different problems in individuals, with symptoms including pain, stiffness, and swelling in the affected areas. Degenerative alterations and osteoarthritis are common, especially in men, and bone ankylosis is more common in men than in women. Women often face longer delays in diagnosis and may experience a higher overall disease burden, including more severe symptoms and lower responses to TNF inhibitors. In contrast, men may show more severe radiographic progression. Despite the differences in outcomes, both genders face significant challenges with this condition. Factors such as genetics, environment, and immunology play a role in the development of AS, with the HLA-B27 molecule being particularly important in the genetic disorder. Hippo signaling in AS regulates TAZ, and downregulation of MST1/2 and NDR1/2 has been observed. Although there are various treatment options, like exercises and physical therapy, not all methods are strongly backed by research. Traditional treatments usually involve anti-inflammatory medications and physical activity, while newer treatments like TNF blockers show promise in managing symptoms. Treatment for AS includes both pharmacological and non-pharmacological methods, with non-steroidal anti-inflammatory drugs being commonly used. Ayurvedic therapy, including Panchakarma treatments and specific medications, has also shown promise in managing AS. Additionally, AS significantly affects foot health and quality of life, highlighting the need for further research and potential treatments.

Keywords: Ankylosing spondylitis, Hippo signaling pathways, therapy, immunity, gender, AS, treatments

Introduction:

The chronic inflammatory condition known as ankylosing spondylitis (AS) affects the axial skeleton and causes gradual deformation of the spine, spondylitis, enthesitis, sacroiliitis, and syndesmophyte growth. (Chee, M., & Sturrock, R. (2007))

Although it typically appears in young adults between the age group of 15-30 (Dougados, M. 2001) with chronic back pain, the diagnosis is often diagnosed five to ten years later because it is tricky to detect and frequently overlooked. Because of AS, a disease called "bamboo spine" may develop, characterized by increased joint stiffness and complete bone fusion. The bamboo spine is a common late symptom of ankylosing spondylitis that affects vertebral connections and puts patients at risk for major problems. (Echchikhi, M., et al. 2020)

It has been suggested that the primary focus of the pathological changes in AS that are inflammatory, traumatic, and degenerative are the entheses, which are the locations where tendons or ligaments get attached to the bone. It is thought that enthesitis is primarily responsible for the painful process of ligament calcification. Enthesitis, a prevalent characteristic of spondyloarthritis (SpA), affects 30 to 50 percent of patients and is characterized by inflammation in the areas where tendons or ligaments join. (Yehudina, Y.D., & Trypolka, S.A. 2021). Enthesitis is linked to lower functional status, increased fatigue, and elevated illness activity in ankylosing spondylitis (AS) patients. (Rezvani, A., Bodur, H., et al. 2014)

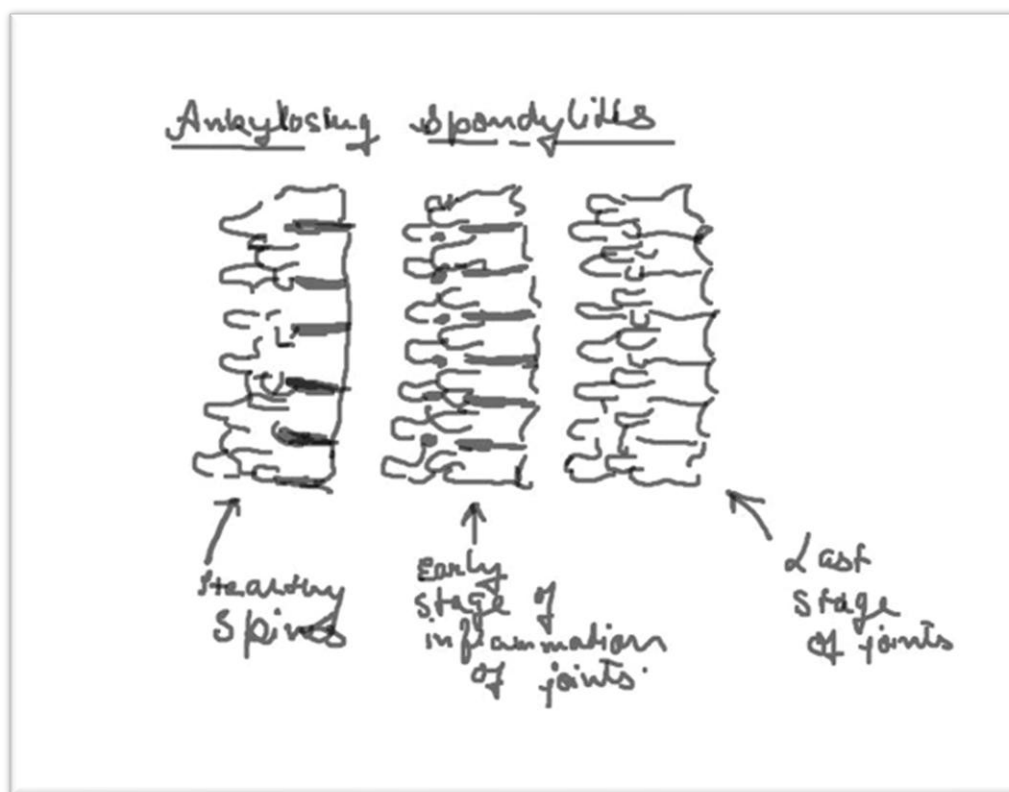


Fig1. Morphologies of the spine of Ankylosing spondylitis with respect to a healthy spine

It may damage the spine and sacroiliac joints, as well as ankylosis (fusion), which may cause the spine to become less flexible and ultimately lose all of its motion. According to Braun A. Ankylosing Spondylitis usually occurs before 45 years (Braun A. et al., 2011) when patients have diminished physical function, a substantial reduction in productivity at work and it may

also worsen the quality of life in the years after the disease's beginning, when adults are at their most productive. (Dagfinrud H et al., 2005)

Gender differences

In general, boys develop slightly earlier and stronger muscles than girls, and adolescents build stronger and more toned muscles at maturity than during childhood. Compared to limb muscles, trunk muscles exhibit larger age and gender variances. During this developmental stage, joint flexibility declines as muscle tone and strength rise. Peripheral joint signs of seronegative enthesopathy and arthropathy (SEA) syndrome typically start in childhood, although spinal manifestations of AS typically start in adolescents and early adults. On the other hand, both the axial and extremities groups often see a decline in muscle tone and strength as people age. The prevalence of AS is in line with trends that show muscle competence declining in later ages for both sexes, peak strength (and tone) increasing in adolescents and early adults, and males more than females.

Endometriosis increases a woman's risk of developing several chronic illnesses, which also include cancer, heart disease, endocrine disorders (hypothyroidism), and, most commonly, autoimmune diseases such as Rheumatoid arthritis (RA), multiple sclerosis, scleroderma, systemic lupus erythematosus, ulcerative colitis, Crohn's disease, Sjögren's syndrome, celiac disease, and autoimmune thyroid. Remarkably, recent studies have shown that endometriosis may increase these women's susceptibility to AS.

Women who are suffering from endometriosis do have a high risk of generating various kinds of chronic diseases which also includes cancer (Kvaskoff M et al., 2015.), endocrine disorders (hypothyroidism), cardiovascular disorders (Rafi U et al., 2023) and, most prominently a numerous autoimmune diseases which do include, multiple sclerosis, Crohn's disease, coeliac disease, systemic lupus erythematosus, scleroderma, ulcerative colitis, Sjögren's syndrome, and autoimmune thyroid disorder (Shigesiet al., 2019) (Zervou MI, Vlachakis D, et al., 2022.). Notably, new research indicates that endometriosis may make these women more susceptible to AS. (Yin Z, Low HY, et al., 2022).

Primary aldosteronism is the most prevailing cause of secondary hypertension. This disorder is typified by elevated aldosterone excretion, decreased plasma renin activity (PRA), low potassium levels (hypokalemia), and high blood pressure (hypertension). According to experimental and clinical research, Aldosterone is a mineralocorticoid hormone essential for controlling electrolyte balance and preserving volume homeostasis. It may also encourage inflammatory harm to specific organs. (GP Rossi, 2011). Thus, chronic inflammatory autoimmune disorders may be exacerbated by aldosterone, which is produced by these proinflammatory effects.

CLINICAL EVIDENCE WITH CASE STUDY: A retrospective analysis examined 25 female patients identified during an assessment of 161 patients with ankylosing spondylitis (AS). Each woman was matched with a male participant with a similar follow-up period (20.7 years for women vs. 17.0 years for men) and age of onset (23.0 years for women vs. 22.2

years for men). Women took an average of 12.8 years to receive an AS diagnosis, compared to 10.3 years for men. Findings revealed that 72% of women and 32% of men had extraspinal arthropathy ($p < 0.05$). Additionally, 40% of women and 16% of men had shoulder arthritis and cervical spine issues (not significant), while 48% of women and 36% of men had peripheral joint disease. Notably, anemia affected 8 women and 2 men ($p < 0.05$), while recurrent uveitis affected 1 man and 10 women ($p < 0.01$). Additionally, compared to 35% of males, 60% of women had relatives with spondylarthritis ($p < 0.05$), indicating a possible sex-linked genetic component to the condition. (Sharp GC, *et al.* 2019)

Case Study

A lady aged around 35 years with a 10-year history of spondyloarthritis (SpA) and four months of neck edema recently showed signs of Mixed Connective Tissue Disease (MCTD), commonly referred to as Sharp's syndrome. Systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, and polymyositis are characteristics of MCTD, a rare systemic illness marked by elevated levels of anti-U1-RNP antibodies. Raynaud's phenomenon, oesophageal hypotonia, hand edema, muscle weakness, and joint pain are typical symptoms. The kidneys, heart, lungs, and central nervous system can all be impacted by severe cases, which are frequently moderate. Pulmonary hypertension is associated with a high death rate. The early diagnosis process is complicated by the absence of defined diagnostic criteria according to Шаяхметова, .Σ., and Ананьева, Л.О. (Sharp GC, *et al.* 2019)

Genetic factors:

Since over 90% of the development risk is assigned to HLA-B27, ankylosing spondylitis is seldom thought of as an inherited condition according to Brown, MA, Kennedy, LG, and others (1997). About 85% to 95% of White and Han Chinese patients suffer from ankylosing spondylitis and over 86% of Hispanic patients have HLA-B27 positive. (2017, Jamalyaria F, Ward MM, *et al.*) But only $\leq 8\%$ of the general population as a whole (Reveille JD, Zhou X, *et al.*, 2019) (Reveille JD, *et al.*, 2009). Spondyloarthritis (SpA) affects only around 5% of those with HLA-B27 in the general population (Khan MA and Akkoc N, 2005). In context to (Zhou X, Reveille JD, *et al.*, 2019) and (Ziade NR, 2017) in North Africa, in the Middle East, and among Black people in the United States the ubiquitousness of HLA-B27 in patients with ankylosing spondylitis (AS) which do vary from about 50% to 84% approximately. Twin concordance rates are not 100%, and over 10% of instances do not involve HLA-B27. It is reported that out of 27 patients, 17 patients are considered in the monozygotic group and similarly 4 out of 15 are in the dizygotic group, the recorded concordance rates for HLA-B27-positive monozygotic twins were 63% and 27%, respectively in the early stages of Ankylosing Spondylitis (AS), the HLA-B27 gene significantly influences the size and degree of sacroiliac joint bone marrow edema lesions. This makes HLA-B27 a crucial factor in the development of ankylosing spondylitis. Bennett and colleagues (2008). The HLA-B27 family, which has 231 protein subtypes and 328 alleles ranging from HLA-B*27:01 to HLA-B*27:232, demonstrates a significant level of genetic variety.

Notably, the variant HLA-B*27:22 was subsequently retracted after being discovered inaccurate. Only a few amino acids separate these subtypes, which may affect the molecule's selectivity in binding peptides. (López de Castro JA, Galocha B, 2010). The ancestral subtype HLA-B*27:05, the most prevalent HLA-B27 subtype, is widely dispersed throughout the world, present in all racial and ethnic groups, and is closely linked to AS.(Dashti N et al., 2018) (Cortes A et al., 2015) (Reveille JD, Zhou X, et al., 2019). The most prevalent categories of HLA-B*27 that include HLA-B*27:02, which is commonly existed in individuals of European, Chinese, and Mediterranean or Northern African ancestry; HLA-B*27:04, primarily present in Eastern Asia and China; HLA-B*27:07, which is observed in Western Asia; and HLA-B*27:15, a subtype derived from HLA-B*27:04 embedded in China. Additionally, other subtypes of HLA-B*27 are positively associated with ankylosing spondylitis (AS) within specific populations.

Less common subtypes, such as HLA-B*27:03 (found in West Africa), HLA-B*27:06 (found in Southeast Asia and derived from HLA-B*27:04) (Van Gaalen FA, 2012), and HLA-B*27:09 (primarily found in Sardinia) (Dashti N et al., 2018), are not linked to AS. The latter two subtypes are occasionally found in patients with AS.

HLA-B*27:05 and its primary subtypes are the source of other, uncommon HLA-B27 subtypes, which are made up of amino acid changes. According to research, those who test positive for particular HLA-B27 subtypes are more likely to get ankylosing spondylitis (AS) and some of its symptoms, such as peripheral joint involvement. Some populations have uveitis (Robinson PC et al., 2015) and (CortesA et al. 2015) (Lin H, Gong YZ, 2017).

There is a lot of research being done on how HLA-B27 contributes to the pathophysiology of AS. Six mechanisms is described in a tabular format have been suggested:

HLA -B27 contributors	Description
CD8+ Natural killer (NK) cells and T-lymphocytes	A peptide that is "arthritogenic" is presented (Faham M. et al., 2017). CD8+ natural killer (NK) cells and T lymphocytes are presented with endogenous peptides from bacteria, viruses, cancer cells, or "self" proteins by the MHC class I molecule HLA-B27. It has proven difficult to pinpoint a particular peptide associated with spondyloarthritis (SpA), despite considerable efforts. Though current research indicates that patients with ankylosing spondylitis (AS) have more inflammatory joints but fewer cytotoxic CD8+ T cells in their peripheral blood, CD8+ T lymphocytes are implicated in the

	pathophysiology of AS. (Gracey E. et al., 2020)
Misfolding in Endoplasmic Reticulum (ER)	In contrast to other HLA-B alleles, heavy chains such as HLA-B27 have a special tendency to misfold in the endoplasmic reticulum (ER). (Navid F. and others, 2021). (Jeanty C. and others, 2014) (Jah N. and others, 2020). One possible explanation for genetic susceptibility is misfolding of HLA-B27, more especially, improper peptide loading and folding. (Navid F. <i>et al.</i>, 2021). In contrast to the non-AS-associated alleles B*27:06 and B*07:02, the HLA-B27 subtypes linked to ankylosing spondylitis (AS)—specifically B*27:02, B*27:05, and B*27:07—exhibited a greater tendency to aggregate in intracellular vesicles derived from the endoplasmic reticulum (ER), according to a study. Both transgenic rats expressing HLA-B27/human β2-microglobulin (hβ2m) and cells from patients with spondyloarthritis (SpA) showed high levels of this aggregation. (Jeanty C. and others, 2014) (Jah N. and others, 2020). ER-associated degradation is the mechanism by which misfolded HLA-B27 heavy chains degrade as a result of their aggregation and misfolding in the endoplasmic reticulum (ER). Pro-inflammatory cytokines, including interleukin (IL)-23 and interferon-gamma, are upregulated as a result of this pro-inflammatory unfolded protein response, which also triggers the innate immune system. Other cytokines, especially those connected to the T helper 17 (Th17) pathway, are also produced more frequently as a result of this reaction. (Navid F. and others, 2021) (Jah N <i>et al.</i>, 2020); (Jeanty C <i>et al.</i>, 2014).
Impact of homodimer due to the presence of a cysteine residue.	At the 67 th position in the α 1 domain there's the presence of a cysteine residue and other places which make HLA-B27 heavy chains notably form homodimers and are more

	prone to self-adhere. These homodimers have been identified on the cell surface and are admitted by leukocyte immunoglobulin-like receptors and KIR (Killer-cell Immunoglobulin-like Receptors). The impact of homodimerization on the risk of ankylosing spondylitis (AS) is yet unclear. This ambiguity is especially noticeable because the self-adhesive feature is shared by HLA-B27 subtypes linked to AS (such as HLA-B*27:02, B*27:04, B*27:05, and B*27:07) and those unrelated to the condition (like B*27:06 and B*27:09). B*27:03 is the exception, as it does not conform to itself effectively. (TCC and Lim Kam Sian, 2019)
Capacity to infiltrate and eliminate arthritogenic microorganisms.	HLA-B27-positive people have alterations in their capacity to infiltrate and eliminate arthritogenic microorganisms. This is most noticeable in reactive arthritis when a compromised ability to destroy intracellular germs leads to bacterial persistence and elevated cytokine production (Sahlberg AS and others, 2012).
CD4+ T cell receptor.	HLA-B27 is recognized as an antigen by CD4+ T cell receptors. This recognition occurs either by inert B27 heavy chains or homodimers (and peptides derived from them) or by the trimolecular complex of $\alpha 2$ microglobulin, a peptide, and the B27 heavy chain. This interaction triggers an autoimmune response. (Boyle LH et al., 2001)
Change in microbiome.	People who test positive for HLA-B27 have a changed microbiome, which influences how susceptible they are to illness.

Table 1. Describes on how HLA-B27 contributes to the pathophysiology of AS.

Other MHC genes excluding HLA-B

Other than HLA-B alleles, also have been associated with AS risk, however far less so than HLA-B27. Research conducted on Black, Han Chinese, and White individuals has revealed a negative correlation between AS development and HLA-B*07, B*35, and B*57, and a positive correlation with HLA-B*40.

(Reveille JD et al., 2019)(Cortes A, Pulit SL et al., 2015) (van Gaalen FA et al., 2013)(Londono J et al., 2015). Peripheral versus axial spondyloarthritis is more likely to occur in those with HLA-B*15. HLA-B*14:03 may make West Africans who are HLA-B27-negative more susceptible to AS (Londono J et al., 2015); African Americans did not exhibit this variant (Reveille JD et al., 2019). An extensive international imputation investigation found an independent association between AS susceptibility and HLA-A*02:01 (Cortes A. et al., 2013). However, a much larger imputation study was unable to substantiate this (Cortes A, Gladman D, et al., 2018). DNA sequencing identified the MHC-related gene MICA in a Han Chinese cohort and linked it to a large group of White American individuals with AS (Zhou X, Wang J et al., 2014). In Taiwanese patient research, AS was likewise associated with HLA-C alleles (Wang CM et al., 2017). After taking into account the linkage with HLA-B27, this was not observed in a larger cohort of white American patients (Reveille JD et al., 2019). Specifically, there were stronger correlations between AS and MHC class II alleles like HLA-DRB1 and alleles at HLA-DPA1 and DPB1. (Reveille JD et al., 2019)(Robinson PC et al., 2015) (Díaz-Peña R et al., 2013)(Huang XF, Li Z et al., 2013). Probably the cause of connections with other MHC loci, particularly TAP and TNF, is the relationship with HLA-B27 haplotypes (Qian Y et al., 2017)(. Ma B, Yang B, et al., 2013).

Other than MHC genes

More than 100 responsive genes or loci outside the MHC locus genes for AS, Crohn's disease, psoriasis, and ulcerative colitis have been found and their activities described by genome-wide association studies. Endoplasmic reticulum aminopeptidase 1 (ERAP1) and interleukin 23 receptor (IL23R) are particularly significant genes; AS patients with HLA-B27 positive blood types are more likely to have ERAP1 than those with HLA-B27 negative blood types. AS susceptibility genes which is noted by gene chip and genomewide association studies, including ERAP1 (Ellinghaus D et al., 2016)(Han R, Xia Q et al., 2018) (Qian Y, Wang G et al., 2017) (López-Larrea C et al., 2002)(Cortes A et al., 2013)(Cortes A, Gladman D et al., 2018)(Díaz-Peña R, Castro-Santos P et al.,2013) (Reveille JD et al., 2010) (Liu J, Pu W et al., 2019) (Lin Z, Bei JX, Shen M et al., 2011)(Tang Y, Yang P et al., 2018) (Cinar M, Akar H et al., 2013) (Wen YF, Wei JC et al., 2014)(Evans DM, Spencer CC et al., 2011)(Seregin SS et al., 2013) (Robinson PC, Costello ME et al., 2015) (Yuan Y et al., 2019) (Ruan WF, Xie JT et al., 2018) (Wang NG, Wang DC et al., 2015) (Zhang X, Li X et al., 2017) (Xia Q, Wang M et al., 2017) (Yang X, Li M et al., 2015) (Zhai Z, Wang Z et al., 2018) (Lee YH, Bae SC et al., 2015) (Liu X, Hu LH et al., 2011) (Aita A, Basso D et al., 2018) (Tsui FW, Tsui HW et al., 2014) (Wang M, Xin L et al., 2017) (Lau MC, Keith P et al., 2017) . Interestingly, a recent study comparing 2752AS patients with acute anterior uveitis (AAU)

with 3836 AS patients without AAU discovered novel associations with AAU. Finding significant molecular pathways that are probably in charge of AS pathogenesis is one of these studies' key accomplishments. Novel therapeutic targets have been seen as a result of this identification. Improved patient and treatment matching may result from an understanding of the genetic variations in AS etiology.

Hospitalization with infections as a child—A Swedish national case-control study found a correlation between the later start of AS and hospitalization for infections in childhood. Of the 10,257 control participants and 2453 AS patients in the study, 17.4% and 16.3%, respectively, had been admitted to the hospital due to an infection before the age of 17 (Lindström U, Exarchou S, et al., 2016). While tonsillitis and respiratory tract infection rates were higher in AS patients than in controls, appendicitis that ties to a lower risk of AS. No correlations were found between AS and any other kind of illness.

Treatment strategy

The treatment options for ankylosing spondylitis (AS) have evolved significantly in recent years. Monthly intravenous infusions of methylprednisolone and pamidronate, together with combination therapy consisting of methotrexate and sulfasalazine, have been effective for patients who do not respond to non-steroidal anti-inflammatory medicines (NSAIDs). (Malaviya, A.N., et al., 2007). Biological treatments, such as TNF inhibitors and IL-17A antibodies, play a crucial role in managing AS symptoms and slowing the progression of the disease (Le, Q.A., Kang et al., 2020). Current guidelines recommend that for patients who do not respond to TNF inhibitors, either secukinumab or ixekizumab should be considered as first-line biologic treatments (Machado, P.M., 2020). However, it's important to note that biological treatments may not be cost-effective at typical willingness-to-pay levels (Le et al., 2020). Exercise and physiotherapy are still important non-pharmacological ways to manage AS (Sari, I., Öztürk et al.). Although routine radiographic monitoring is not advised, disease activity can be tracked using imaging techniques such MRI (Machado, P.M., 2020). Anti-inflammatory drugs and exercise continue to be the mainstays of traditional treatment for active ankylosing spondylitis, however tumor necrosis factor blockers are thought to be safe and beneficial (Zochling, J., & Braun, J., 2005). Physical therapy, patient education, NSAIDs, and biologics that block TNF-alpha are non-surgical methods of treating AS (Sangala, J.R., et al. 2008).

The latest developments in treating Ankylosing Spondylitis:

In recent years, the options for treating ankylosing spondylitis (AS) have changed significantly. When non-steroidal anti-inflammatory medicines (NSAIDs) are ineffective for a person, a combination therapy that includes methotrexate, sulfasalazine, and monthly intravenous infusions of methylprednisolone and pamidronate has been shown to be effective (Malaviya et al., 2007). Biological therapies, particularly TNF inhibitors and IL-17A antibodies, play a crucial role in managing AS symptoms and slowing the progression of the disease (Le et al., 2020). According to current guidelines, if patients do not respond to TNF

inhibitors, the first-line biologic treatments should be secukinumab or ixekizumab (Machado, 2020). However, it is important to note that biological treatments may not always meet the standard willingness-to-pay criteria in terms of cost-effectiveness (Le et al., 2020).

Additionally, diagnostic methods have advanced. For instance, MRI is now utilized to detect inflammatory changes in the axial spine and sacroiliac joints, enabling earlier diagnosis. These advancements offer the potential for pain relief and may delay disease progression as seen in radiographic evaluations (Liu et al., 2004; Brown & Bradbury, 2017).

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