

Ankylosing spondylitis: recent breakthroughs in diagnosis and treatment

Saeed A. Shaikh, MD, FRCPC, FACP*

Ankylosing spondylitis (AS) is generally easy to diagnose when the characteristic findings of the “bamboo” spine and fused sacroiliac joints are present on radiographs. Unfortunately, these changes are usually seen late in the disease after tremendous suffering has been incurred by the patient. Diagnostic delay averages seven to ten years. Historically, once the diagnosis was made, the treatment options were often inadequate or poorly tolerated in many individuals. This condition most often starts in early adulthood when people are typically in the earlier stages of their careers, resulting in diminished workforce participation and decreased quality of life. If an individual has a family physician, this might be the first encounter with a healthcare provider. Quite often, the initial practitioner is sought at a public walk-in clinic or chiropractic office.

In recent years, there have been two major developments in the management of AS that make earlier diagnosis possible and offer the hope of alleviating pain and preventing structural changes that result in loss of function. These developments include the use of magnetic resonance imaging (MRI) to visualize the inflammatory changes in the sacroiliac joint and the axial spine, and the demonstration that tumor necrosis factor (TNF) blocking agents are highly efficacious in reducing spinal inflammation and possibly in slowing radiographic progression.

This review outlines diagnostic strategies that can help identify AS in its earlier stages. Special attention is

La spondylite ankylosante (SA) est en général facile à diagnostiquer quand les constats caractéristiques de la colonne de « bambou » et des articulations sacro-iliaques fondues apparaissent sur les radiographies. Malheureusement, ces changements sont perçus trop tard dans l'évolution de la maladie, après que le patient ait connu de terribles souffrances. Les moyennes de délais du diagnostic sont de sept à 10 ans. Dans le passé, une fois le diagnostic posé, les options de traitement étaient souvent inadéquates ou plutôt mal tolérées chez plusieurs malades. La maladie se manifeste en général au début de l'âge adulte, quand les personnes en sont aux premières étapes de leur carrière, leur condition provoquant une diminution de leur contribution à l'équipe au travail et une baisse de leur qualité de vie. Si une personne a un médecin de famille, cela pourrait être la première rencontre avec un fournisseur de soins de santé. Assez souvent, la personne se mettra à la recherche d'un praticien initial ou on se rendra à une clinique sans rendez-vous ou à un bureau de chiropraticien.

Au cours des dernières années, il s'est présenté deux importants développements dans la gestion de la SA qui rendent possible un diagnostic précoce et offrent l'espoir de soulager la douleur et empêcher des changements structurels qui se traduisent par une perte de fonctions. Ces percées dans la médecine comprennent l'utilisation de l'imagerie par résonance magnétique (IRM) pour visualiser les changements inflammatoires dans l'articulation sacro-iliaque et l'épine axiale et la

* Assistant Professor, Department of Medicine, Division of Rheumatology, McMaster University, Hamilton, ON, Canada.

Contact information: Saeed A. Shaikh, 589 Lake Street, suite 204, St. Catharines, ON L2N 7L6, tsshaikh@aol.com

Tel: 905-937-2220, Fax: 905-937-4404.

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focused on treatment advances, including the use of anti-TNF agents, and how these medications have been incorporated into clinical recommendations for daily use. (JCCA 2007; 51(4):249–260)

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Introduction

Ankylosing spondylitis (AS) is the prototype disease within the spondyloarthropathies (SpA), a group of diseases presenting mainly with inflammation of the axial skeleton, peripheral arthritis and enthesitis (inflammation at insertion sites of bone to tendons, ligaments, and joint capsules). This disorder is in fact a systemic disease, causing numerous extraskelatal manifestations that have a significant influence on patient prognosis. Included among these accompanying features are inflammatory bowel disease, acute anterior uveitis (iritis), and psoriasis. In addition, there is a strong association with the HLA-B27 antigen and a familial aggregation.

It is estimated that AS affects about 0.5% of the population and male to female ratio is roughly 2:1.^{1–3} In comparison, rheumatoid arthritis is seen in about 1% of most populations.⁴ Ankylosing spondylitis most commonly has its onset while a patient is in their twenties, although late teenage years are also relatively common for initial symptoms.⁵ The disease onset is at a younger age and acute iritis is more common in B27 positive as compared to B27 negative patients.⁶ In a study of 1080 patients (90% HLA-B27 positive), the average age of onset in B27 positive patients was 24.8 years, whereas in those that were B27 negative it was 27.7 years.⁵ It is very unusual to have a patient present with this disorder beyond forty-five years old. A common diagnosis that is mistaken for AS in the more advanced aged groups would be diffuse idiopathic skeletal hyperostosis (DISH). In this condition, the sacroiliac joints are typically spared and

démonstration que les agents bloquants du facteur de nécrose des tumeurs (TNF) sont très efficaces pour réduire l'inflammation et peut-être ralentir la progression radiographique.

La présente étude décrit les stratégies de diagnostic qui peuvent aider à identifier la SA à des étapes antérieures. Une attention spéciale cible les percées dans le traitement, y compris le recours à des agents anti-TNF et la façon dont les médicaments sont incorporés dans les recommandations cliniques dans le quotidien. (JACC 2007; 51(4):249–260)

mots clés : spondylite, diagnostic, premiers soins

there is usually a more flowing and bulky ossification of the anterior longitudinal ligament, rather than the syndesmophytes of AS that bridge between the vertebral body corners and include the annular fibers of the intervertebral discs.

The objectives of this paper will be to provide rationale for more early and accurate diagnosis of AS, despite the difficulties associated with radiographs and the lack of a single pathognomonic clinical feature or laboratory test. In addition, updates in management, including the newer anti-tumor necrosis factor (TNF) agents, will be discussed.

Clinical

Inflammatory back pain

The main symptom of AS is inflammatory back pain (IBP). There are several features that can help differentiate IBP from mechanical low back pain (MLBP). The value of the clinical history in differentiating IBP from MLBP has been investigated and refined by Rudwaleit and colleagues, by comparing the clinical history of 213 patients (101 with AS and 112 with MLBP) younger than 50 years who had chronic back pain.⁷ The features that are most helpful in differentiating IBP from MLBP are outlined in Figure 1.

This analysis yielded a sensitivity of 70.3% and a specificity of 81.2% if 2 of these 4 parameters were fulfilled (positive likelihood ratio 3.7). If 3 of the 4 parameters were fulfilled, the positive likelihood ratio increased to 12.4.⁷ Importantly, none of the single parameters alone

<i>1. morning stiffness of >30 minutes' duration</i>
2. improvement in back pain with exercise but not with rest
3. awakening because of back pain during the second half of the night only
4. alternating buttock pain

Figure 1 *Features in the clinical history differentiating inflammatory back pain from mechanical low back pain.*

sufficiently differentiated AS from MLBP. In contrast, several sets of combined parameters proved to be well balanced between sensitivity and specificity.

Apart from affecting the complete axial skeleton, AS can also involve peripheral joints. Often the ribcage joints such as the costovertebral and costotransverse articulations and less often the manubriosternal and costochondral junctions may be involved, and this can result in pain with coughing or sneezing as well as local tenderness. The more common joints affected include the hips and shoulders. Patients with concomitant psoriasis tend to get more peripheral joint involvement.

Enthesitis

The concept of enthesitis has emerged as an important contributor to the inflammatory process involved in AS. Inflammatory cell infiltrates invading the adjacent bone at the enthesis (bony sites of ligamentous attachments) have been well described.⁸ Bone marrow changes have also been observed in the vertebrae of some AS patient.⁹ Magnetic resonance imaging (MRI) using fat suppression techniques has confirmed that the extracapsular changes taking place in inflamed synovial joints of patients with AS commonly involve the entheses.¹⁰ In the spine, enthesitis occurs at capsular and ligamentous attachments at discovertebral, costovertebral, costotransverse, and facet joints. Involvement can also be present at the bony attachments of interspinous and supraspinous ligaments. Some of the more common peripheral enthesal sites that can be affected are located around the shoulders, hips, and the plantar fascia and Achilles insertions on the calcaneus.

Extraarticular manifestations

Acute anterior uveitis (also referred to as iritis) is a well recognized feature associated with AS and one or more attacks are seen in 20–40% of AS patients.^{11–12} The typi-

cal presentation is a sudden onset of eye pain, redness, visual blurriness, and photophobia. Some cases can be chronic and lead to permanent visual impairment. Psoriasis is seen in about 9% and inflammatory bowel disease (Crohn's disease and ulcerative colitis) in up to 6% of those with AS.^{13–14} Both of these co-morbidities seem to be associated with more severe AS disease activity and poorer functioning.¹⁵ There are also several associated cardiovascular features, such as aortic insufficiency, conduction abnormalities, and an increased risk of myocardial infarction.^{16–18} Patients with AS are at an increased risk of sustaining vertebral compression fractures because of a heightened incidence of osteoporosis, spinal rigidity, and kyphosis. A population-based study in Minnesota found that the prevalence of thoracolumbar compression fractures in AS sufferers was 7.6 times higher compared with the population rates.¹⁹ Another study revealed that 47% of the vertebral compression fractures in AS patients resulted in some form of neurological complication ranging from transient paresthesia to loss of strength in a limb.²⁰

Disease burden

In addition to the obvious deleterious effects on quality of life, there is also a substantial economic burden associated with AS. When looked at in a large Canadian study, the mean annual overall costs associated with the disease was CDN\$9,008, with indirect cost accounting for 38% of the total. Total costs increased with diminishing physical function as measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). For example, a BASFI >7 resulted in mean annual costs of CDN\$23,300.²¹ Longer disease duration, increased age, and smoking have been shown to be associated with decreased functioning.²² The indirect costs related to AS are mostly from disability payments due to withdrawal from the

workforce in addition to early retirement.²³ Contrary to previous beliefs, the condition doesn't 'burn out' over time, but instead typically continues to be active for decades.²⁴ However, the majority of loss of function occurs in the first ten years from disease onset.²⁴ The burden of this disease in terms of reduced quality of life, risk of unemployment, and overall direct and indirect healthcare costs are similar to rheumatoid arthritis.²⁵ However, since AS usually starts in early adulthood, there is a longer overall disease duration when compared to aged-matched patients with rheumatoid arthritis. Therefore, AS patients have to adjust to their disease for most of their lives.

Making the diagnosis earlier – where chiropractors can make a difference

Back pain is the predominant reason for a referral to a chiropractor. The prevalence of sacroiliac joint disease in lumbar spine and AP pelvis x-rays taken at the Canadian Memorial Chiropractic College has been studied.²⁶ Findings showed that 23.2% of the cohort had degenerative changes in the sacroiliac joints compared to 3.8% having definite criteria for sacroiliitis consistent with AS. Another 4.1% had possible inflammatory changes (<Grade II bilateral sacroiliitis). The inflammatory changes were more prevalent in male patients and those with a younger mean age.²⁶

Making a diagnosis of AS can be challenging.²⁷ It is quite common for the diagnosis of AS to be missed or markedly delayed,²⁸ particularly in the primary care setting.²⁹ On average, there is a 7–10 year delay in the diagnosis of this disease from the onset of symptoms.⁵ There are a number of factors that contribute to the delay in diagnosis. First, the majority of back pain sufferers do not seek care from healthcare providers. Young men tend to be the segment of the population that are the least likely to do so. When care is sought, the most common source is a general practitioner or chiropractor.³⁰ Since AS has a predilection to affect young males, these findings would suggest that a substantial amount of sufferers do not even get assessed. Second, the existing criteria, namely the modified New York Criteria, requires advanced radiographic changes to be present in the sacroiliac joints.³¹ Unequivocal sacroiliitis of at least grade 2 bilaterally or grade 3 unilaterally plus clinical symptoms is required before a diagnosis of ankylosing spondylitis can be made. These changes usually lag several years after the onset of axial pain and stiff-

ness, despite the presence of inflammation as detected by MRI. Thus, the established classification criteria for AS is more suited for picking up advanced disease.

In order for chiropractors or other practitioners to make a more accurate diagnosis of axial SpA in its early stages (pre-radiographic AS), there are certain clinical features that have been proven to increase the disease likelihood. These features have been assigned probabilities and a diagnostic algorithm has been devised by Rudwaleit, et al.²⁸ As a starting point, a 5% prevalence of axial SpA among patients with chronic LBP presenting to their primary care provider was used. Apart from radiographic sacroiliitis, some of the clinical features that increased the likelihood of axial SpA were: positive MRI (likelihood ratio [LR] of 9.0), positive HLA-B27 (LR = 9.0), history of acute iritis (uveitis) (LR = 7.3), positive family history (LR = 6.4), and a positive response to NSAIDs (LR = 5.1).²⁸ In the assessment it would be important for the chiropractor to assess for characteristics of inflammatory back pain (see Figure 1) and clinical features such as uveitis, positive family history of SpA, response to NSAIDs, peripheral joint swelling, or presence of inflammatory bowel disease or psoriasis.

The role of MRI in diagnosis

Recent use of MRI has confirmed that active inflammation is present in the spine and/or sacroiliac joints long before the appearance of unequivocal changes of sacroiliitis on plain radiographs.³² Therefore the absence of radiologic sacroiliitis should not rule out the diagnosis of AS. Magnetic resonance imaging is now clearly established as a sensitive and specific tool to detect sacroiliitis.^{33–34} MRI findings include a decrease in signal intensity in the subchondral marrow on T1-weighted images, whereas an increase in signal intensity is seen on T2-weighted images. These changes represent inflammation of edematous tissue. Blum and colleagues demonstrated that when used to detect active sacroiliitis, MRI was 95% (20 out of 21) sensitive and 100% (43 out of 43) specific, whereas plain radiography was only 19% (4 out of 21) sensitive and 47% (20 out of 43) specific.³³ MRI has also helped define the role of enthesitis in the evolution of the pathology in the early stages of SpAs.³⁵ Fat-suppressed MRI techniques have detected an inflammatory response involving the soft tissues and underlying bone marrow in an extensive area around the entheses. MRI has also provided in-

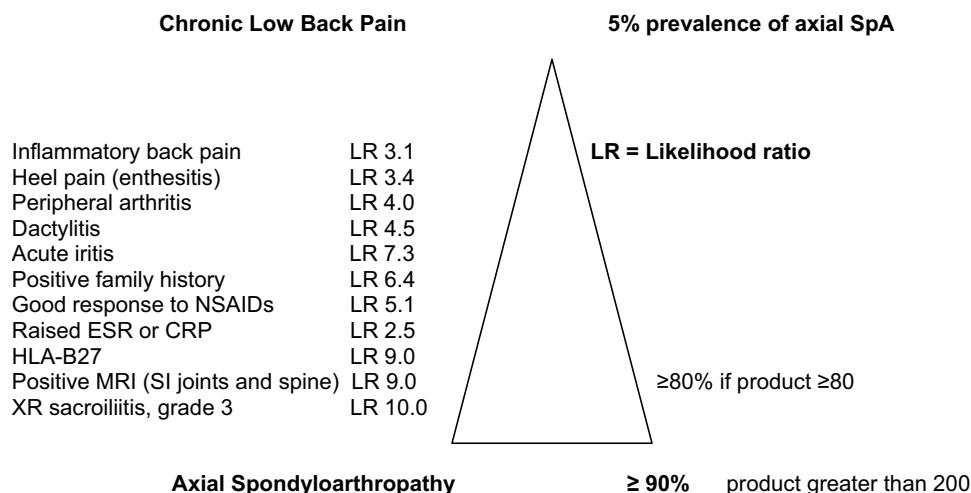


Figure 2 Disease probabilities of the presence of axial spondyloarthritis (SpA) according to the presence of individual SpA parameters in individual patients. The prevalence (pretest probability) of having axial SpA among patients with chronic back pain is 5%. To calculate the disease probability for an individual patient, the likelihood ratios (LRs) of the parameters that are present in the patient are multiplied, resulting in an individual LR product. Thus, the resulting LR product depends on both the number of parameters present and the LR of the parameters present. If the LR product is 80, the disease probability will be 80%, and if the LR product is 200, the disease probability will be >90%. A disease probability of 90% or more is regarded by us as definite disease.

NSAIDs: nonsteroidal anti inflammatory drugs; MRI: magnetic resonance imaging; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SpA: spondyloarthropathy

From: Rudwaleit, et al. *Ann Rheum Dis* 2004; 63:535–43, with permission.

formation to suggest the observed synovial and cartilage changes in SpAs are mainly due to an enthesal rather than synovial-based pathology.³⁵ The main use for MRI in the management of AS is in establishing early diagnosis and with distinguishing active inflammatory axial disease from non-inflammatory causes. An example would be the patient with inflammatory back pain who does not have definite radiologic sacroiliitis. An MRI can show inflammation, bone marrow edema, and pre-radiographic erosions at the sacroiliac joints. The short-tau inversion recovery (STIR) technique is able to show these changes well without having to use the addition of the added cost of gadolinium enhancement.³⁶ Computerized tomography is more accurate than plain radiography for morpho-

logical changes in the sacroiliac joints but cannot differentiate active from inactive disease.^{37–38}

Management

Until recently treatment options for AS have been limited. Physical therapy techniques and non-steroidal anti-inflammatory drugs (NSAIDs) have been the mainstay of therapy in these patients. No real disease modifying anti-rheumatic treatment was previously available. There are multiple therapies such as methotrexate, sulfasalazine, and leflunomide that have proven efficacious in rheumatoid arthritis. However, all of these have failed to provide substantial benefit from the often disabling axial symptoms and signs of AS.^{39–41} Therefore, a previous delayed

diagnosis did not have the same perceived adverse consequences because of the lack of highly effective therapeutic choices.

Some patients with milder forms of the disease can achieve success with exercise and physical therapy.^{42–45} There is consistent evidence in the form of randomized, placebo controlled trials to show that NSAIDs and cyclooxygenase-2 specific inhibitors (coxibs) are superior to placebo in improving spinal pain.^{46–51} In addition, NSAIDs may have a protective effect on structural damage when taken on a regular basis.⁵² Safety concerns, particularly with gastrointestinal (GI) bleeding and cardiovascular toxicity limit the use of these agents in many patients.^{53–55} These side effects appear to be dose-dependent.⁵⁶ Despite traditional management approaches (education, exercise, physical therapy, and NSAIDs) remaining important, there are a sizeable proportion of patients that will continue to do poorly. In a German study conducted in 2000, there were 1080 AS patients who replied through questionnaires. Seventy-eight percent had regularly taken NSAIDs for their disease 12 months prior to the study. 19.1% reported complete pain control, 26.8% reported pain reduction to one quarter, and a further 34.4% reported pain reduction to one half. However, over 20% of patients taking NSAIDs still reported insufficient pain control and more than 40% changed the NSAID due to lack of efficacy. One quarter of AS patients reported severe side effects from their treatment, most commonly abdominal pain, headache, dizziness, and nausea. The percentage of AS patients reporting changing their NSAID due to side effects ranged from 10.5% for celecoxib to 31.4% for indomethacin.⁵⁷ Another study, from the United Kingdom, involving 246 participants with AS, revealed that 64% of the respondents had a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score greater than 4 out of 10. The group of patients with BASDAI scores above 4 correlated with greater pain scores (assessed with a 0–10 cm VAS composite score), higher BASFI scores (worse functioning) and poorer quality of life scores compared to those AS patients with a BASDAI below 4.⁵⁸ These studies underscore the need for more effective treatments. Apart from being ineffective or poorly tolerated many of the above modalities offer little help in arresting or delaying the progression of the disease.⁵⁹ Consequences of poor disease control may include diminished quality of life,

which extends into the context of work disability and early retirement.

New treatment approaches

Since 2000 considerable progress has taken place in the therapeutic approach to SpA. This progress is due in large part to the development of effective biologic therapies and to improved clinical trial design and implementation. TNF-alpha blocking agents (monoclonal antibodies or soluble receptors) are the first representative drugs, of which the indication has recently been expanded to also encompass patients with AS. TNF-alpha is a pro-inflammatory cytokine that is involved in the pathogenesis of AS and related SpA, in addition to psoriasis, and inflammatory bowel disease.⁶⁰ It appears to be key in the inflammatory response observed in AS. The detection of an abundance of TNF messenger RNA has been documented in synovial biopsies from sacroiliac joints in patients with AS (Figure 3).⁶¹

Most recently, it has been convincingly demonstrated that the TNF-alpha blocking agents infliximab, etanercept, and adalimumab have a strong and prompt effect on almost all features of AS. All three of these medications have demonstrated their benefits in large-scale randomized, double-blind, placebo-controlled trials.^{62–64} These agents now make it possible to suppress disease activity, improve physical function, and slow disease progression. It is worthwhile noting that the AS patients that have been studied in these large-scale studies were those whose disease was refractory to NSAIDs and physical therapy. In addition, the studied patients in these trials were required to have active disease, demonstrated by a BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) greater than 4.

Infliximab is given as an intravenous infusion every six to eight weeks. In addition to the benefits on the axial and peripheral joint symptoms, there are also beneficial effects on those with concomitant inflammatory bowel disease (IBD), uveitis, and psoriasis.^{65–67}

Etanercept is given as a subcutaneous injection, weekly or biweekly. It also is highly effective for the signs and symptoms of AS. There is the added benefit of it being effective in psoriasis, however it is less useful for the symptoms of IBD and uveitis.

Adalimumab is dosed every other week in the form of a

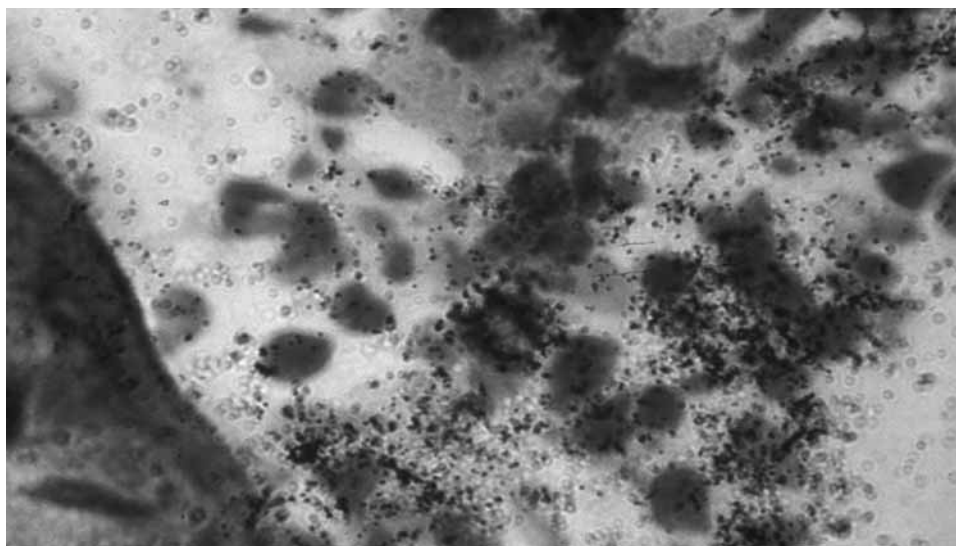


Figure 3 The detection of mRNA (dark staining) of tumor necrosis factor-alpha in a sacroiliac joint biopsy from a patient with ankylosing spondylitis.

From: Braun J, et al. *Arthritis Rheum* 1995; 38:499–505, with permission.

subcutaneous injection. Like Infliximab, it is effective in psoriasis and IBD.⁶⁸ At the moment, insufficient information is available regarding uveitis.

There is now long term evidence to support anti-TNF treatment. Infliximab has demonstrated efficacy and safety for up to five years in an open-label study of patients with moderate to severe AS.⁶⁹ In this study, a durable sustained response was observed, with the mean BASDAI score prior to treatment being 6.4 and after five years it was 2.5. Impressively, 34% of the patients were in clinical remission. In the placebo-controlled studies, there is two year evidence for infliximab and etanercept and one year for adalimumab.^{70–72}

In addition, to spinal pain and stiffness, there is also notable improvement with peripheral arthritis and enthesitis. Clinical indicators of disease activity, such as juxta-articular bony inflammation that can be seen by MRI, can be suppressed quite dramatically by TNF-alpha blockers.^{73–75} (see Figure 4) Less radiographic progression after 2 and 4 years of continuous treatment with infliximab compared to conventional therapy has been suggested in a small continuous study.^{76,77} The erythro-

cyte sedimentation rate (ESR) and C-reactive protein (CRP) are acute phase reactants in blood serum that may be raised in patients with AS when the disease is more active. Both the ESR and CRP also tend to be lowered with this class of medications.^{61–63}

There is some data that suggests that AS patients with a short disease duration and younger age are more likely to respond to TNF-alpha blocking agents.⁷⁸ Thus, underscoring that an early and reliable diagnosis of AS has now become an important and very relevant issue. In all of the larger studies, major side effects were low and minor side effects were mostly in the form of mild infections, although opportunistic infection such as the reactivation of tuberculosis can be more common.⁷⁹ Infusion and injection site reactions can also occur but are generally quite manageable. Patients with a history of a solid organ malignancy or melanoma may not be appropriate candidates for TNF blockers because of a lack of information on experience with these subgroups.

Patient access to the anti-TNF therapies is somewhat restrictive, mostly because of the associated high costs of the medications. It is common practice to file applications with private health insurance plans or with provin-

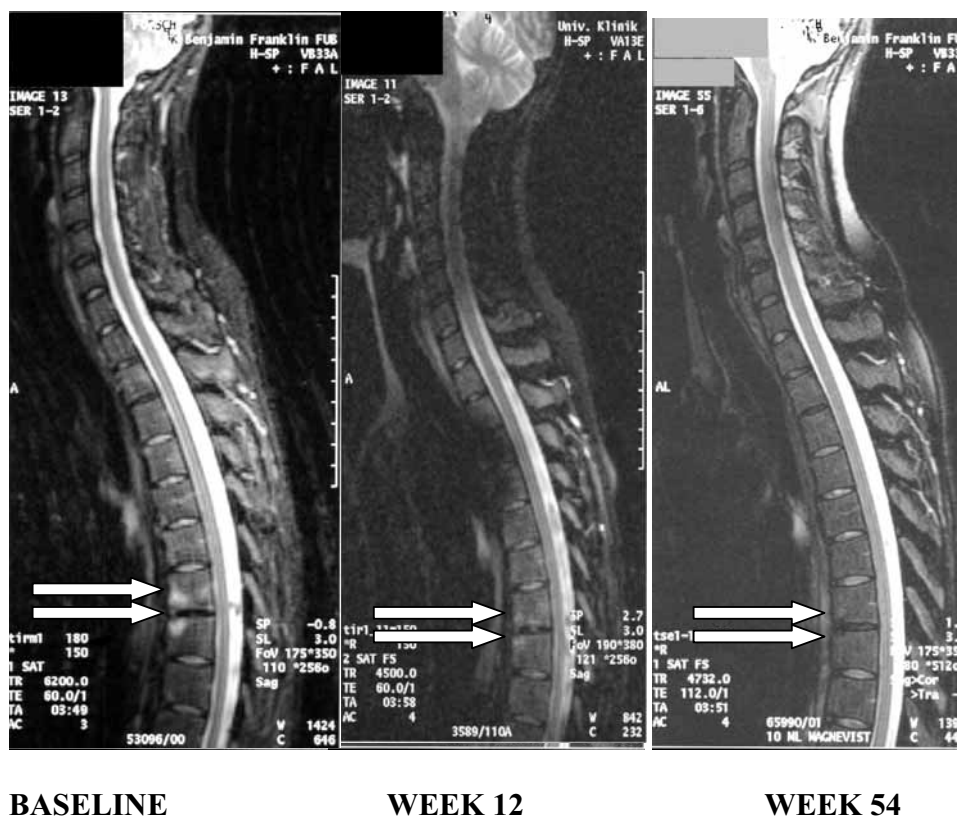


Figure 4 MRI of the spine in the sagittal plane using T2-STIR sequences that incorporate suppression of normal marrow fat signal. Abnormal increased signal on the STIR sequence represents increased concentration of “free water” otherwise referred to as “bone marrow edema.” This abnormal signal represents inflammation. Consecutive upper and lower anterior endplates of vertebrae are shown (arrows) at baseline and then after 12 and 54 weeks of treatment with Etanercept. Note the improvement of the inflammatory lesions seen at the endplates.

MRI: Magnetic resonance imaging.

Images courtesy of Maksymowych WP, Lambert RGW, University of Alberta website (altarheum.com), with permission.

cial health ministries in Canada to obtain anti-TNF agents. This process usually requires the cooperation and know-how of a rheumatologist.

Conclusions

Now that there are medications that are highly effective in treating AS, it is more of a priority to diagnose this condition earlier. There are now proposed clinical path-

ways to make an earlier diagnosis prior to established radiographic changes becoming present.²⁸ It is important to differentiate inflammatory from mechanical back pain symptoms. Moreover, consideration should be given to some of the extraskelletal manifestations, such as uveitis, inflammatory bowel disease, and psoriasis that when present can be helpful in determining the likelihood of a person having AS. MRI of the sacroiliac joints and spine

also has a role in diagnosis in earlier stages of the disease when inflammation can be detected at a time when radiographs usually appear normal or equivocal.

The AS patient that fails conservative measures and NSAIDs, is the one that needs to be identified and considered for anti-TNF therapies as second-line treatments. The evidence shows that, unlike RA, the so-called “disease modifying” drugs like methotrexate, sulfasalazine, and leflunomide have proven to be ineffective in AS. The TNF blocking agents currently available, infliximab (Remicade), etanercept (Enbrel), and adalimumab (Humira), are approved for the treatment of AS in Canada. We are now in an era where not only symptoms can be targeted, but slowing down and possibly achieving clinical remission of a disease is possible. The implementation and follow up care should be undertaken by an experienced healthcare provider such as a rheumatologist specialized in their use, because of the specifics involved with drug access, tools to measure response to therapy, and the monitoring of potential side effects.

Chiropractors have a significant role to play in Canada's health care system in addressing the burdens of disease related to back pain, particularly with respect to AS. This includes the primary care setting where chiropractors, in making an earlier diagnosis differentiating inflammatory back pain from mechanical back pain are able to facilitate the AS patient's best interest.

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