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Review Article

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Ankylosing Spondylitis-A review on Drug Promotion through the Ages

Suhasishray

Consultant orthopedic and Spine Surgeon, Woodlands Multispecialty hospital, Kolkata, India

***Corresponding author**
Dr. Suhasishray, In-charge Spine surgery-Department of Orthopaedics and Spine Surgery, Ramakrishna Mission seva Pratisthan and Vivekananda Institute of Medical Sciences, Kolkata, India.

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Abstract

The diagnosis of ankylosing spondylitis is often delayed due to ambiguous clinical manifestations and strict diagnostic criteria. However, imaging techniques such as magnetic resonance imaging have been found effective for the early diagnosis of non-radiographic sacroilitis. New tumor necrosis factor alpha (TNF-α) inhibitors have good efficacy for patients with persistently high disease activity despite conventional nonsteroidal anti-inflammatory drug treatment which are effective in low diseases cores. Thus, early diagnosis and aggressive treatments are essential for ankylosing spondylitis patients. Though the disease can be stayed with conventional DMARDs and NSAIDs in low score diseases, in high score diseases TNF-α inhibitors are more effective. In this review, we discuss new diagnostic criteria for ankylosing spondylitis, administration methods of TNF-α inhibitors, comparative review between conventional AS drugs and TNF-α inhibitors and the long-term follow-up results for patients treated with TNF-α inhibitors.

Keywords: Ankylosing Spondylitis, Medical Treatment, TNF-α inhibitors, Comparative Review.

Introduction

Ankylosing spondylitis is a chronic disease that involves axial joints, eventually causing deformity and ankylosis of the spine and joints [1]. The disease often involves the hip and shoulder joints, and surgical treatments are required if severe joint contracture is found. Accurate assessment of the range of hip movement is critical for better understanding of disease progression considering that1/3 of the patient's present symptoms with. Ankylosing spondylitis involves other organs and affects the life quality of patients via accompanying dactylitis (25- 50%), uveitis (25-40%), inflammatory bowel disease (26%), and psoriasis (10%) [2]. Although the Etiology of the disease is yet to be elucidated, human leukocyte antigen (HLA) B27 is one of the Most important factors; the prevalence rate o fHLA-B27-positive patients ranges from 0.4% to 1.4% depending on patients' ethnicity [3].

The onset of ankylosing spondylitis occurs mostly between the ages of 20 to30 years; its diagnosis can be delayed by 5-6years [4]. So far, ankylosing spondylitis has been diagnosed mainly on the basis of the modified New York criteria [1]. However, development of new diagnostic criteria is warranted because early detection of inflammation in the sacroiliac joint is now possible through advanced diagnostic technologies (e.g., magnetic resonance imaging [MRI]). Such early detection of inflammation is since an innovative early treatment approach using potent biological agents has been introduced, development of new diagnostic criteria became an important issue [5].

Recognizing this need, the Assessment of Ankylosing Spondylitis (ASAS), a group of experts in Ankylosings pondylitis, provided diagnostic criterion and treatment guidelines in 2016.

- Clinical criteria:
  - Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest.
  - Limitation of motion of the lumbar spine in the sagittal and frontal planes.
  - Limitation of chest expansion relative to normal values correlated for age and sex.
- Radiological criterion:
  - Sacroiliitis grade ⩾2 bilaterally or grade 3–4 unilaterally.

Definite AS if the radiological criterion is associated with at least one clinical criterion

Figure 1: Modified New York criteria for diagnosing Ankylosing Spondylitis

A recent report indicated that MRI is able to detect sacroilitis on average 7.7 years earlier than x- Ray imaging, indicating that the modified New York criteria may not be suitable for early detection [6]. Furthermore, even though spondyloarthritis does not meet the modified New York criteria, the disease burden is similar to that of ankylosing spondylitis and both diseases exhibit favorable clinical outcomes in response to recently developed biological agents, emphasizing the necessity of new diagnostic criteria [7,8].

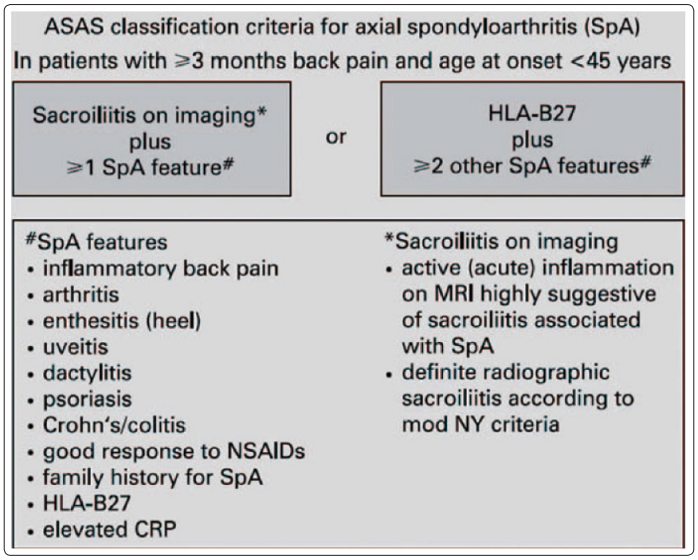

Figure 2: ASAS classification criteria for axial spondyloarthritis
ASAS: Assessment of Ankylosing Spondylitis,
NSAIDs: Nonsteroidal anti-inflammatory drugs,
HLA-B27: Human leukocyte antigen B-27,
CRP: C-reactive protein,
Mod NY criteria: modified New York criteria.

The Goal of Treatments

The progress of ankylosing spondylitis varies; however,1/3 patients progress with serious disability. In the early stage of the disease, back pain and ankylosis are often found as well as a Limitation of chest expansion and reduction in the motion range of the spine, which cause Occupational disability and director in direct economic burden [4].

The objectives of treatment are:

1. Alleviation of pain,
2. Recovery of physical functions related to daily life and occupational activities, and
3. Delay of structural damage responsible for physical impairments.

Medications

(a) Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs including the Coxib class are the first-line drugs for ankylosing spondylitis. A recent study reported that ankylosing spondylitisis associated with the prost a gland in Ereceptor 4 (PTGER4) gene. This receptor is associated with bone absorption; NSAIDs inhibit prostaglandin production, thus reducing the absorption [9]. It is difficult to choose the best NSAID agent since responses and therapeutic potency vary between patients. Although it has been controversial which administration method is the most effective, it is now generally accepted that the drugs should be administered it is important to note that there are several complications of NSAIDs, in particular related to the cardiovascular system as well as gastrointestinal and renal complications. However, patients with symptoms not related to joints (e.g., inflammatory gastrointestinal disorders) may be treated with the selective COX-2inhibitors without risk of complications [10].

It is possible to use two different types of NSAIDs with in the maximum allowed dosage over at least 4weeks, but no specific regulations are available for the duration of each NSAID. For instance, it is possible to use NSAIDA for a week and replace it with NSAIDB for the remaining 3weeks; similarly, one NSAID can be used for 2 weeks and another one for the following 2weeks. If the Bath Ankylosing spondylitis disease activity index (BASDAI) is higher than 4 even after NSAID Treatment (i.e, no improvement in symptoms), other agents such as TNF-α inhibitors should be Considered (Figure 3) [11].

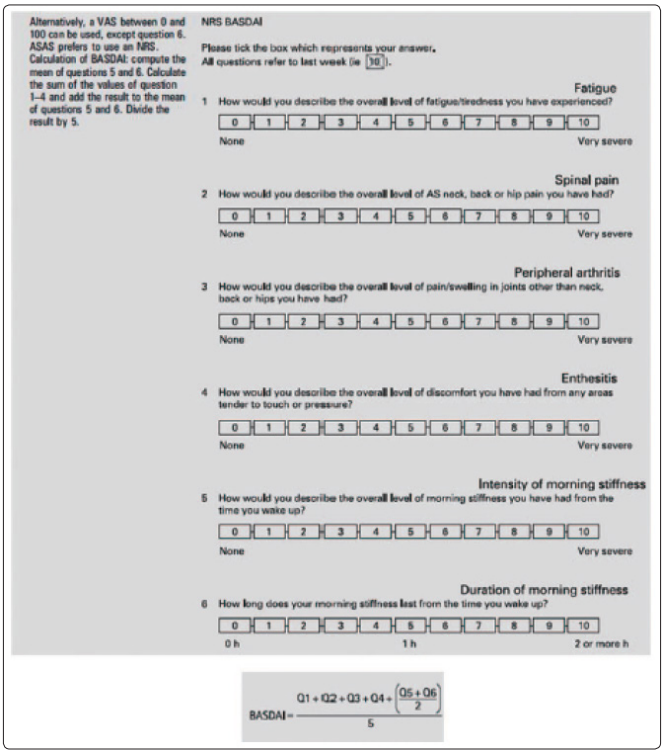

Figure 3: Numerical rating scale of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

VAS: visual analogue scale, ASAS: Assessment of Ankylosing Spondylitis, NRS: numeric
Rating scale, AS: ankylosing spondylitis.

(b) Analgesics

Acetaminophen and opioid- (like) agents are often used:
(1) for patients who complain of pain Even after administration of NSAIDs and TNF-α inhibitors or 2)when other therapeutic options are not available.

(c) Glucocorticoids

Although local glucocorticoid injection can be considered for skeletal muscle inflammation such asenthesitis, systematic administration of steroids is not generally recommended [11].

(d) Disease-Modifying anti – Rheumatic drugs (DMARDs)

Although the administration of DMARDs (e.g., sulfasalazine and methotrexate) is not recommended for axial diseases such as back pain, sulfasalazine is worth considering for treatment of peripheral arthritis [11].

(e) TNF-αinhibitors

In1995, Braun and coworkers isolated TNF-α from ankylosings pondylitis patients via sacroiliac arthrocentesis [12]. Thus, it was recognized that TNF-α is an important inflammatory mediator in this

disease, which dramatically facilitated the development of biological agents. As many studies have demonstrated that TNF-α inhibitors are effective for treatment of not only advanced ankylosings pondylitis, but also its early stage, early use of TNF-α inhibitors has been recommended [2-5, 7,8, 11]. The ASAS guidelines (first released in 2006) recommended to use them for patients who had been diagnosed with ankylosings pondylitis according to the New York criteria and treated with more than two NSAIDs over 3 months.

Yet, in the updated ASAS guidelines (2010), axial spondyloarthritis was included in addition to the New York criteria. Furthermore, it was recommended to use the TNF- inhibitors in cases where more than 2 types of NSAIDs are administered over 4 weeks [11]. So far, infliximab, etanercept, and adalimumab have been used in South Korea. In the present review, we introduce the dosing methods for clinical applications of these three agents on the basis of recently reported long term follow-up studies [13-16].In the following we introduce some principles of application of TNF-α inhibitors.

1. Even though there is no difference in potency of various TNF-α inhibitors against musculoskeletal system symptoms in ankylosings pondylitis, monoclonal antibodies (infliximab and adalimumab) have been found to be more effective for gastrointestinal symptoms than receptor blockers (etanercept).
2. If one agent is not effective, it can be replaced with other agents.
3. Responses to biological agents should be evaluated at least 12 weeks after administration.
4. Favorable outcomes of treatment with TNF-α inhibitors are expected if (1) duration of symptoms is short and (2) the result of C-reactive protein examination is positive.
5. Latent tuberculosis should be examined before administration since some reports indicate that the incidence rate of tuberculosis is elevated due to TNF-α inhibitors [17].

Infliximab (Remicade)

Infliximab is a chimeric monoclonal antibody against TNF-α and is the first developed biological agent, consisting of 75% of human and 25% of mouse sequences [13]. This antibody directly binds to TNF-α and neutralizes it. It is administered by intravenous injections at 5mg/kg body weight. For the first administration, the same dose of infliximab is injected twice with an interval of 2 weeks and then the drug is administered every 6weeks. Baraliakos et al. Reported a drug survival rate (patients who completed 8years of treatment) of 48% and 88% of partial remission or low disease activity after 8-year follow-up. It was also reported that the potency was similar when the treatment was interrupted for 3 years and then resumed [13]. In addition, the authors reported that responses after the first 12 weeks of treatment could be use d as a prognostic factor for clinical outcomes after 8years. Finally, it was claimed that the stability of the antibody was not an issue of concern.

Etanercept (Enbrel)

Etanercept is a soluble blocker of TNF-α. This fusion protein binds TNF-α,which hinders Interactions between TNF-α and TNF-α receptor located on other cells. Etanerceptis generally administered by subcutaneous injection of 25mg twice a week [14,15]. Martl´n-Molaet al. reported that 63% of the enrolled patients completed 5years of etanercept administration without any serious complications, while Baraliakos et al. [14,15] Reported a drug survival rate of 62%, partial remission in 31% of patients, and complete remission in 44% of patients in a7-year follow-up study. Similar to infliximab, etanercept was effective when medication was interrupted and then resumed; the drug survival rate was slightly higher in the etanercept group than in the infliximab group.

Adalimumab (Humira)

Like infliximab, adalimumab is amonoclonal antibody against TNF-α but its sequences 100% human. Adalimumab is administered by subcutaneous injections Sieperetal [16]. Reported a drug survival rate of 65%, partial remission according to Ankylosing Spondylitis Disease Activity Score (ASDAS) in 51% of patients, and ASDAS inactive disease in 61% of patients in a 5-years follow-up study. Similar to the long-term follow-up results for infliximab, favorable outcomes of long-term follow-up were demonstrated with remission achieved after12 weeks of administration. Although there is no alternative option available if TNF-α inhibitors are not effective, other biological agents such as inhibitors of inflammatory cytokines (e.g., interleukin [IL]-1andIL-6) have been actively investigated [18].

Duration of medications

The optimal duration of ankylosing spondylitis treatment with NSAID sand TNF-α inhibitors is still controversial. According to the recommendations of ASAS published in 2010, continuous administration of NSAIDs is recommended only when the disease is persistently active or symptomatic, but the same paper suggested that continuous treatment would be more effective for prevention of new bone formation than on demand treatment [11]. A recent review reported no significant difference in safety and efficacy between on demand and continuous administration of NSAIDs against inflammatory arthritis, but further investigations are warranted [19]. Long-term follow-up studies have reported no noticeable difference in the potency of TNF-α inhibitors when they were administered continuously or intermittently, suggesting the necessity of on-demand administration [13,15]. Overall, it seems reasonable to assess the benefits and risks of continuous administration of NSAIDs and TNF-α inhibitors. In particular, administration of TNF-α inhibitors may be discontinued for a certain period of time and then resumed. Such scheme might be useful under special circumstances, for example:

1. A patient wants to become pregnant,
2. A patient has been suffering from repetitive infections, and
3. A patient is about to have surgery [19,20].

Conclusion

Although there are limited options available for diagnosis and treatment of ankylosing spondylitis, early detection and treatment of this disease have been made possible by recent dramatic advances in diagnostic technologies and biological agents. Although surgical treatment is sometimes used, most ankylosings pondylitis patients are treated with medications at non orthopedic departments. Overall, orthopedic surgeons should make more effort to reduce the economic burden of ankylosings pondylitis and alleviate patients'suffering from spinal and musculoskeletal pain and deformity via active diagnosis and treatment [21-23].

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