Treatment of Ankylosing Spondylitis

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ABSTRACT. Ankylosing spondylitis (AS) is a condition characterized by inflammatory back pain and associated with considerable disability and diminished quality of life in affected individuals. The condition is undertreated in part due to a delay in diagnosis and limited therapeutic interventions. Although traditional treatment approaches (physical therapy, exercise, patient education, nonsteroidal antiinflammatory drugs) remain important components of the management of AS, the demonstrated efficacy of tumor necrosis factor-α (TNF-α) antagonists such as etanercept and infliximab have allowed clinicians to more effectively manage this condition. These targeted therapies have demonstrated rapid and consistent effectiveness in reducing the axial and peripheral symptoms of AS, slowing disease progression, and improving patient function and quality of life. Appropriate and timely use of TNF-α antagonists offers additional options for patients with active AS who are inadequately controlled with conventional treatment. (J Rheumatol 2006;33 Suppl 78:24-31)

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INTRODUCTION

Ankylosing spondylitis (AS) is an inflammatory condition whose main clinical feature is inflammatory back pain caused by sacroiliitis and spondylitis[1]. Patients with AS may also have peripheral arthritis, enthesitis, and acute anterior uveitis[1]. AS is associated with considerable disability, reduced quality of life, and high costs in terms of direct medical expenses and indirect costs due to lost wages and productivity[2-7]. Patients with AS report similar pain and functional disability as those with rheumatoid arthritis[2], and leave the labor force at a 3-fold higher rate than the general population[8].

Until recently, the options available to clinicians for the treatment of AS have been limited, with patient education, physical therapy, and nonsteroidal antiinflammatory drugs (NSAID) being the mainstay of effective therapy. The advent of tumor necrosis factor-α (TNF-α) antagonists represents a breakthrough in the treatment of AS. Nonetheless, despite the development of these more effective treatments that can slow AS disease progression, there is still an unmet need in the management of this condition due to the suboptimal use of these therapies. This article will review the treatment of AS.

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UNDERTREATMENT/SUBOPTIMAL TREATMENT

As discussed elsewhere in this supplement series, the diagnosis of AS is frequently missed or substantially delayed, particularly in the primary care setting[9]. Disease onset is insidious, making diagnosis difficult before the occurrence of irreversible damage[10]. A mean delay of 10 years from time of first symptoms to a definitive diagnosis has been reported[11,12]. This delay also means a delay in treatment, allowing significant disease progression to occur.

In patients with AS, severe spinal restriction (< 3 cm of lumbar movement and < 20° of cervical thoracic movement) occurs in up to 41% of patients, and the majority (81%) of these patients are severely restricted within 10 years of onset[13]. It has also been shown that spinal progression is a function of disease duration[14]. Therefore, management of the early stages of AS is critical for slowing disease progression.

TRADITIONAL APPROACHES TO TREATMENT

Both nonpharmacologic and pharmacologic interventions are important in the management of AS. Important nonpharmacologic components of AS management include physical therapy, exercise (including muscle conditioning along with instruction), and encouragement of appropriate posture[15]. Exercise/physical therapy programs have been shown to improve measures of pain, spinal mobility, patient function, and well-being, with supervised programs being more effective than individual at-home programs[16-22]. For example, in a randomized trial in 144 patients with AS, supervised group physiotherapy (hydrotherapy, exercises, and sporting activities) was more effective at improving spinal mobility, fitness,

and patient reported global health than an individualized program[20]. In addition, patient education/support programs have been shown to improve patient perception of well-being[23,24]. For example, a short intensive course (12 hours of education over 2 consecutive days) with sessions on AS disease information, exercises, posture, and home checks for monitoring mobility produced improvements in depression and self-efficacy (daily ability to manage pain, fatigue, and physical functioning) at 3 weeks, with a trend toward continued improvement at 6 months[23]. The frequency and range of types of exercise both significantly decreased over time, underscoring the importance of continued followup and reinforcement of exercise programs in the AS population.

NSAID are the foundation of management of AS, and are currently the first-line drugs for initial management of pain and stiffness. In mostly short-term studies (up to 3 months), conventional NSAID produced significant improvements in symptoms in patients with AS, including spinal pain, duration of morning stiffness, night pain, immobility, stiffness, and peripheral pain[25-37].

More recently, selective cyclooxygenase-2 (COX-2) inhibitors have been evaluated in patients with AS[38,39]. Although etoricoxib is no longer available, a 6-week study in 387 patients with AS treated with etoricoxib 90 mg/day or 120 mg/day showed similar efficacy (spine pain, functionality, and patient global assessment of disease activity) to naproxen 1000 mg/day, and both agents had significantly greater efficacy than placebo[38]. These improvements were maintained over a 52-week double-blind continuation of the 6-week study[38]. Similarly, 6 weeks of treatment with celecoxib 100 mg twice daily showed similar efficacy to ketoprofen 100 mg twice daily and significantly greater efficacy than placebo in terms of global pain intensity and functional impairment in 246 patients with AS[39]. After 6 weeks of therapy, patients were randomly assigned either continuous or as-needed treatment with celecoxib 100 mg twice daily for 2 years (allowed to increase to 200 mg twice daily at patient's discretion)[40]. Despite a similar effect on measures of pain, inflammation, and spinal mobility, continuous use of celecoxib (or other NSAID taken continuously) slowed radiographic progression to a significantly greater degree than intermittent use after 2 years[40].

Disease modifying antirheumatic drugs (DMARD) are a potential second-line therapy but their efficacy in AS is unproven. There has been a lack of consistent results in clinical trials with DMARD[41-47]. Sulfasalazine has generally demonstrated efficacy at improving AS-associated peripheral arthritis, but not back pain[42,48,49]. For example, a 36-week study of 264 patients with chronic long-standing AS (mean duration 18.5 years) reported no significant differences between sulfasalazine 2000 mg/day and placebo recipients for any clinical measures of efficacy, including physician and patient global assessment, morning stiffness, back pain, night pain, duration of morning stiffness, spondylitis functional index, and joint pain/tenderness[49]. Another study showed some improvement in clinical symptoms (morning stiffness and chest expansion) relative to placebo following 26 weeks of treatment with sulfasalazine ≤ 3000 mg/day[50]. However, a subgroup analysis in patients with AS reported no significant difference in axial response rates between sulfasalazine and placebo in patients with axial disease only or in patients with combined axial/peripheral disease, but did show a peripheral response in patients with axial/peripheral disease[49]. In a combined analysis of patients with seronegative spondyloarthropathies (264 AS, 221 psoriatic arthritis, and 134 reactive arthritis), sulfasalazine produced better treatment response rates (composite index of 4 outcome measures) in patients with peripheral arthritis than in those with exclusively axial disease[48].

Methotrexate (MTX) also has not demonstrated consistent efficacy for AS-associated back pain, and has shown inconsistent efficacy for peripheral disease[41,47,51]. In a small study (n = 51), there were no significant differences in efficacy observed between naproxen and MTX plus naproxen after 1 year[47]. Another small study (n = 35) showed some benefit with MTX therapy over placebo after 24 weeks for a composite index of improvement [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Health Assessment Questionnaire for Spondyloarthropathies, severity of morning stiffness, physical well-being, and physician and patient global assessment of disease activity], with a statistical difference between the 2 groups observed only at Week 24[51]. Both of these studies used relatively low dosages of MTX (7.5 mg/wk).

Leflunomide was not effective for axial manifestations of AS, but may provide some benefit for peripheral arthritis. In a 6-month open-label study in 20 patients with AS, treatment with leflunomide (100 mg/day for 3 days, then 20 mg/day for 6 months) did not produce significant improvement in a number of measures, including BASDAI, BASFI, patient and physician global assessment, Medical Outcome Study Short Form-36 General Health Survey (SF-36) mental component, and C-reactive protein[52]. Significant improvement in peripheral arthritis, as assessed by the mean number of inflamed joints, was noted in this study.

NEW APPROACHES TO TREATMENT

With the advent of biologic agents, it is now possible to slow disease progression in AS rather than simply allay symptoms. TNF-α is a proinflammatory cytokine involved in the pathogenesis of AS and other spondy-

Table 1. Summary of randomized, placebo-controlled trials of tumor necrosis factor-α inhibitors in patients with ankylosing spondylitis.

Study	No. of Patients (study duration)	Primary Efficacy Endpoint	Results, %	p vs Placebo
Etanercept 25 twice weekly				
Gorman[63]	40 (4 mo)	Composite index responders (20% improvement in 3 of 5 outcome measures*)	Etanercept 80 Placebo 30	0.004
Brandt[64]	30 (6 wks)	≥ 50% improvement in BASDAI	Etanercept 57 Placebo 6	0.004
Calin[67]	84 (12 wks)	ASAS20 responders	Etanercept 60 Placebo 23	< 0.0001
Davis[66]	277 (24 wks)	ASAS20 responders	Etanercept 57 Placebo 22	< 0.0001
Infliximab 5 mg/kg at weeks 0, 2, and 6, then every 6 weeks				
Braun[70]	35 (12 wks)	≥ 50% improvement in BASDAI	Infliximab 53 Placebo 9	< 0.0001
van den Bosch[71]	40 (12 wks)	Global disease activity (0-100 mm) scale	Patient assessment: Infliximab 18 mm Placebo 69 mm	≤ 0.001
			Physician assessment: Infliximab 16.5 mm Placebo 72 mm	≤ 0.001
van der Heijde[72] (ASSERT)	279 (24 wks)	ASAS20 responders	Infliximab 61.2 Placebo 19.2	< 0.001
Adalimumab 40 mg every other week				
Davis[59] (ATLAS)	315 (24 wks)	ASAS5/6 criteria	Adalimumab 44.2 Placebo 13.1	≤ 0.001

*Duration of morning stiffness, degree of nocturnal spine pain, BASFI, patient global assessment of disease activity, and score for joint swelling. ASAS20: 20% improvement in the Assessments in Ankylosing Spondylitis response criteria; ASAS5/6: ASAS questions 5 and 6 criteria; ASSERT: Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy; ATLAS: Adalimumab Trial Evaluating Long-Term Efficacy and Safety in AS; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

loarthropathies[53,54]. Etanercept and infliximab are TNF-α antagonists approved by the US Food and Drug Administration for the treatment of AS[55,56], and both drugs have demonstrated rapid and sustained efficacy in the treatment of this condition. Adalimumab[57] is another TNF-α antagonist in development for the treatment of AS, with preliminary evidence of similar efficacy[58-62].

Etanercept. Etanercept 25 mg twice weekly has demonstrated consistent efficacy in a number of clinical trials in patients with AS (Table 1). In a 4-month study, the percentage of responders (composite index of outcome measures) was significantly higher in etanercept than placebo recipients (80% vs 30%; p = 0.004)[63]. In a 6-month extension of this trial in which all patients received etanercept, these results were maintained in the original etanercept group and patients who had originally received placebo achieved an 80% response rate within 1 month of initiating etanercept treatment[63]. Similar results were observed in a 24-week study, which had a 6-week placebo-controlled portion followed by 6 weeks of continued treatment in the etanercept group and 12 weeks' treatment with etanercept in the placebo group (all patients received 12 weeks' total therapy with etanercept)[64]. Patient function, spine mobility, and quality of life improved with treatment, and one-third of patients experienced a partial remission [Assessments in Ankylosing Spondylitis (ASAS) criteria] after 12 weeks of etanercept treatment. After drug cessation, 75% of patients experienced relapse of symptoms within 3 months[64]. A 54-week open-label extension of this study was conducted in 26 patients who had discontinued etanercept per study protocol (for a mean 26.8 weeks) and who had developed high disease activity[65]. Eighty-eight percent of patients were still receiving etanercept at the end of the extension period, 58% had a ≥ 50% improvement in BASDAI, and 31% were in partial remission[65]. These results are consistent with the results obtained in the initial 12-week study[64].

The proportions of 12-week responders (ASAS20) were similar in 2 larger studies of etanercept (Table 1)[66,67]. All ASAS components, including spine mobility and patient

global assessment, were significantly improved with etanercept treatment. In a large AS study (n = 277), 24 weeks of treatment with etanercept produced a significantly higher percentage of ASAS20 responders than placebo (57% vs 22%; p < 0.0001)[66]. An open-label extension of this study showed sustained efficacy with etanercept treatment: 70% of patients who had previously received etanercept and 78% of patients who had previously received placebo achieved an ASAS20 response at 96 weeks[68]. Spinal magnetic resonance imaging (MRI) has also shown that etanercept treatment produces regression in spine inflammation (improvement of 54% at 12 weeks)[69].

Infliximab. Infliximab 5 mg/kg at Weeks 0, 2, and 6 (and then every 6 weeks thereafter in studies with a duration > 12 weeks) demonstrated consistent efficacy in patients with AS for a number of different primary efficacy measures (Table 1)[70-72]. In the study presented by Braun, *et al*, partial remission was observed in about 20% of infliximab-treated patients compared with about 3% of patients in the placebo group[70].

The longterm efficacy of infliximab for AS has been evaluated in an open-label extension of the Braun, *et al*[70] study. Patients continued to receive infliximab 5 mg/kg every 6 weeks after the induction dosing phase; data for 54 weeks[73], 102 weeks[74], and 156 weeks[75] are available. Of the 69 patients who entered the open-label extension, 54 continued to receive infliximab at 54 weeks[73]. Forty-seven percent of patients who had received continuous infliximab and 51% of patients who received placebo for 12 weeks followed by infliximab were BASDAI50 responders at Week 54, and partial remission was reported in 18% and 17% of patients, respectively[73]. These results were maintained in the 49 patients who completed 102 weeks of the study (41% and 49%, respectively)[74], and in the 46 patients who completed 156 weeks (47% and 43%, respectively)[76]. An assessment of 41 patients from the 2-year analysis[74] showed a slowing of radiographic damage in infliximab-treated patients relative to an untreated cohort[77].

In the large Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) study (n = 279), 24 weeks of treatment with

Table 2. Summary of European guidelines and United States modifications for the use of tumor necrosis factor-α inhibitors in patients with AS. Adapted from the Spondylitis Association of America[15], with permission; and updated based on 2006 ASAS guidelines by Braun, *et al*[84].

ASAS	US Modifications
Diagnosis	
Modified New York criteria	Modified New York criteria
Disease Activity	
BASDAI score > 4 (0–10) scale) and Physician Global Assessment by "expert" opinion, yes/no	BASDAI score > 4 (0–10) scale) and Physician Global Assessment of ≥ 2 on Likert scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe
Previous Treatment	
Failure by lack of response or intolerability to > 2 NSAID for 3 mo for all clinical 3 presentations: axial, peripheral arthritis, and enthesitis. Patients with peripheral arthritis also having a lack of response to sulfasalazine. Patients with enthesitis must have failed appropriate local treatment	Failure by lack of response or intolerability to > 2 NSAID for 3 mo for all clinical 3 presentations: axial, peripheral arthritis, and enthesitis. Patients with peripheral arthritis must have had a lack of response or intolerability to > 1 DMARD (sulfasalazine preferred) for peripheral arthritis. Not required for axial disease or enthesitis (corticosteroid injection not required)
Dosing	
Etanercept 25 mg SQ twice a week or 50 mg once weekly* Infliximab 5 mg/kg IV every 6-8 weeks	Etanercept 25 mg SQ twice a week or 50 mg once weekly Infliximab 5 mg/kg IV every 6-8 weeks
Responder Criteria	
50% improvement of BASDAI or absolute change of 2 on 0–10 cm scale and "expert" opinion	Improvement in BASDAI by at least 2 units and Physician Global Assessment of > 1 unit
Time of Evaluation, wks	
6 to 12	6-8
TB Precaution	
Use country-specific guidelines	TB screening and treatment per American Thoracic Association recommendations

*The 50-mg once weekly alternative dosing regimen has not yet been approved in Europe for AS. On February 23, 2006, this dose for AS was recommended for approval by the Committee for Medicinal Products for Human Use. ASAS: Assessments in Ankylosing Spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; DMARD: disease-modifying antirheumatic drug; IV intravenously; NSAID: nonsteroidal antiinflammatory drugs; SQ: subcutaneously; TB: tuberculosis.

infliximab produced a significantly higher percentage of ASAS20 responders than placebo (61.2% vs 19.2%; $p < 0.001$), and demonstrated significant improvement in a number of other measures, including BASDAI, BASFI, chest expansion, and the physical component score of the SF-36[72]. Recent 30-week data indicated that infliximab in combination with MTX produced significantly greater reductions in BASDAI scores than MTX alone in 42 patients with AS, and significantly greater regression in enthesitis/osteitis as assessed by MRI[78]. The addition of MTX did not appear to extend the dosing interval for infliximab, however, as evidenced by the occurrence of disease flares 8 weeks after the last infliximab infusion[78].

Adalimumab. Adalimumab, another TNF-α antagonist, is under investigation for the treatment of AS. In a small ($n = 14$) open-label 20-week study, adalimumab 40 mg every other week produced significant improvement in spinal symptoms in patients with AS[79]. Preliminary results of the phase 3 Adalimumab Trial Evaluating Long-Term Efficacy and Safety in AS (ATLAS) in 315 patients showed that a significantly higher proportion of adalimumab (40 mg every other week) than placebo recipients achieved ASAS partial remission status (21.6% vs 6.5%) and ASAS5/6 criteria (44.2% vs 13.1%) (both $p \leq 0.001$)[59].

Safety. In the clinical trials discussed above, the TNF-α antagonists were well tolerated, with the rates of adverse events generally being similar in active drug and placebo groups. Injection site reactions, upper respiratory tract infections, and accidental injury were reported in significantly more etanercept- than placebo-treated patients[66]. Infliximab was generally as well tolerated in the large AS study: elevated transaminase levels were reported in more infliximab than placebo recipients[72]. Although the rate of infusion reactions was similar for infliximab and placebo in this AS study, clinical studies have reported a higher rate of this adverse event in infliximab-treated patients[56]. The adalimumab data from the ATLAS study were published in abstract form, and no specific adverse event details were provided for these AS patients (adverse events were comparable between the adalimumab and placebo groups)[59].

General precautions with the use of TNF-α antagonists include (1) an increased risk of opportunistic infections, possible increased risk of lymphoma, and hepatotoxicity (infliximab); and (2) avoidance of use in patients with pre-existing demyelinating disease or moderate to severe heart failure[55-57,80,81]. Rare cases of tuberculosis have been reported in patients receiving TNF-α antagonists, including etanercept[55]. Infliximab and adalimumab carry a black-box warning highlighting the risk for tuberculosis[56,57].

Guidelines for use of TNF-α antagonists. There are a number of published treatment guidelines for biologic therapies in AS[15,82-85]. Many patients with AS meet the criteria for anti-TNF-α treatment (reflecting severe disease) in established guidelines, but do not receive these agents[86]. Recently, a survey of AS patients indicated that nearly two-thirds of patients had poor functional status and quality of life (BASDAI score ≥ 40) and would meet the British Society of Rheumatology criteria for TNF-α antagonist use[86]. The results of this survey, conducted between 2001 and 2003 (just as biologics were being introduced for AS), suggested that there may be a substantial unmet need for effective treatment in AS.

An overview of guidelines for the use of TNF-α antagonists, including the US modifications of European guidelines, is presented in Table 2[15,84].

CONCLUSIONS

Ankylosing spondylitis is associated with significant pain, functional disability, and diminished quality of life. This disease represents a therapeutic challenge for clinicians because of its insidious onset that often results in delays in recognition. Radiologic damage may occur early in the course of AS, underscoring the importance of early recognition and appropriate treatment. The major goal of therapy of inflammatory conditions such as AS is to slow disease progression and improve function.

Conventional approaches to the management of AS, such as physical therapy, exercise, patient education, and NSAID therapy remain important components of AS treatment. Traditional DMARD, such as sulfasalazine and MTX, have not consistently shown benefit, particularly for axial manifestations. The development of targeted anti-TNF therapies that provide disease control has heralded a new era for the treatment of AS and provided hope for many patients suboptimally controlled. Etanercept and infliximab, the 2 TNF-α antagonists currently approved for the treatment of AS, have demonstrated rapid and consistent effectiveness in reducing the axial and peripheral symptoms, and improving patient function and quality of life. Data are also available to support the longterm use of these agents. The established efficacy and safety profiles of the TNF-α antagonists makes this class of agents an important new addition to the previously limited armamentarium available to rheumatologists for the treatment of AS.

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