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Measurement and Treatment of Radiographic Progression in Ankylosing Spondylitis: Lessons Learned from Observational Studies and Clinical Trials

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Abstract

PURPOSE OF REVIEW—One of the major goals of treatment of ankylosing spondylitis (AS) is to prevent or slow the development of spinal new bone formation. Recent observational studies are compared to results from clinical trials for the effects of tumor necrosis factor-alpha inhibitors (TNFi) and nonsteroidal anti-inflammatory drugs (NSAIDs) on radiographic measures of spinal damage.

RECENT FINDINGS—Data from clinical trials indicate that treatment up to 2 years with TNFi was not associated with a difference in rates of progression of spinal damage, compared to historical controls. These studies were based on open-label extensions, and analyzed as cohort studies. Recent observational studies have suggested that TNFi may reduce radiographic progression. The different conclusions may be related to the longer treatment and observation period of these observational studies, which may have permitted detection of changes in this slowly evolving process. There is emerging evidence from a clinical trial and retrospective studies that continuous NSAID use may slow radiographic progression.

SUMMARY—Lack of evidence that TNFi slow radiographic progression in AS in data from clinical trials may be due to the design of these studies, and possibly not a true null treatment effect.

Keywords

ankylosing spondylitis; radiographic progression; measurement; treatment

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory arthritis of the axial skeleton [1]. The natural history of AS is characterized by new bone formation detected on radiographs as

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sacroiliac fusion, syndesmophytes along the rim of vertebral bodies, and fusion of zygapophyseal and costovertebral joints. The accumulation and bridging of syndesmophytes may ultimately lead to ankylosis of the spine, and in 40% of patients, complete spinal fusion [1]. The rate of spinal new bone formation in AS tends to be slow, often taking several decades to progress to complete spinal fusion [1–4].

The major goals of treatment of AS are to alleviate pain and stiffness, maintain good posture, and prevent radiographic progression. Imaging with magnetic resonance imaging (MRI) and plain radiography serves both diagnostic and prognostic purposes [5–7]. MRI can detect changes due to active sacroiliitis and spinal inflammation before plane radiography can detect changes due to chronic damage [8, 9]. Despite the frequent development of syndesmophytes at sites of previous spinal inflammation, syndesmophytes may also originate at areas devoid of recognized inflammation [10, 11]. The precise association between inflammation and new bone formation is not completely understood and is an area of active investigation.

Tumor necrosis factor-alpha inhibitors (TNFi) are highly effective in treating the symptoms of pain and stiffness in patients with AS, as well as signs of active inflammation on MRI [12–15]. The results of clinical trials raised expectations that TNFi would not only alleviate the symptoms of AS and active spinal inflammation, but would also prevent or slow the development of subsequent radiographic damage. However, the capacity of TNFi to slow radiographic progression was not demonstrated in data drawn from clinical trials [16–19]. These results contrast with more recent data from two observational studies, which reported data supporting the effectiveness of TNFi to slow radiographic progression, raising questions about the impact of the study design on the observed difference in radiographic outcomes, rather than an effect of drug therapy itself [20, 21]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also widely used in the treatment of AS, and may also reduce radiographic progression based on results of a clinical trial and a retrospective cohort study [22, 23]. The main findings of these recent studies are summarized in Table 1, and detailed below.

RADIOGRAPHIC SCORING METHODS

Radiographic progression in AS has been assessed using changes visible on plain radiographs. Several radiographic scoring methods to quantify spinal damage have been developed and validated [24–26]. Compared to the original Stoke Ankylosing Spondylitis Spine Score (SASSS) and the Bath Ankylosing Spondylitis Radiology Index (BASRI), the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) is currently considered the radiographic scoring method of choice [27]. In the mSASSS, the anterior corners of the cervical and lumbar vertebrae are scored for erosions, sclerosis, squaring (scored as 1), syndesmophytes (scored as 2), or bridged syndesmophytes (scored as 3), with a possible range of 0 (normal) to 72 (complete bridging of both the cervical and lumbar spine). The mSASSS detects a higher proportion of patients with radiographic progression at 4 years than the BASRI (43% vs. 18% at the lumbar spine; 41% vs. 23% at the cervical spine). Changes of ≥ 1 unit at 2 years were observed in 46.4% of patients using the mSASSS,

25.2% using the BASRI, and 38.1% using the SASSS. Group mean mSASSS increase approximately 1 unit per year [27].

Given its higher sensitivity to detect change, the mSASSS has been used in clinical studies to evaluate the effectiveness of treatments to slow radiographic progression. Nonetheless, the mSASSS, as all radiographic scoring methods, may be limited by poor visualization due to patient positioning, penetration, or overlying structures, and is dependent on accurate interpretation of images by human readers.

CLINICAL TRIALS OF TNFi

No controlled trials have been done that compare TNFi and placebo for their ability to slow radiographic progression in AS. Placebo-controlled trials in AS have all had durations of 24 weeks or less, a time too short to detect any change in structural damage on radiographs. However, data from open-label extensions of controlled trials have been used to address this question. In the first study in this line of investigation, 257 patients enrolled in a 24-week double-blind placebo-controlled trial of etanercept 25 milligrams twice weekly were followed for an additional 72 weeks with open-label treatment [16]. Changes in mSASSS from the start of the trial to the end of the open-label period were compared to changes in a historical cohort of patients with AS that had radiographs taken with an interval of 2 years. Patients in both groups had a similar duration of AS (10 to 11years) and similar mSASSS at baseline (16 and 14 for the etanercept-treated and control groups, respectively). The mean change in mSASSS over the 2 years of observation was just under 1 mSASSS point in both groups.

In a careful consideration of the data, the authors acknowledged that differences in AS activity may confound the comparison between these groups, particularly if the historical cohort included mostly inactive patients who may have less propensity to progress. They therefore identified a subset of the historical cohort matched on AS activity to those in the etanercept trial. Changes in mSASSS in this subset were also similar to those in the etanercept-treated group, indicating that differences in AS activity did not likely account for the null findings. There were also no differences by the duration of etanercept treatment, between clinical responders and non-responders, or by NSAID use. The authors concluded that the progression of structural damage in AS was independent of TNF-mediated inflammation.

Although the comparison was not based on a randomized allocation to treatment, and thus the potential for unmeasured confounding exists, the groups appeared similar in many relevant characteristics. The study did not specify the clinical effect to be detected and the statistical power of the study to detect an effect of that magnitude, but the similarity of the changes indicates that the sample size was not a limitation accounting for the null results. Radiographs were read blinded to patient group and temporal sequence, as they would in a clinical trial. Blinding to temporal sequence may explain why the degree of change in mSASSS in both groups was somewhat lower than that seen in previous observational cohorts. Eleven percent of patients in the etanercept group were missing follow-up radiographs, and data for these were imputed. Of those in the etanercept group, 24% had less

than 48 weeks of treatment, and 50% had less than 72 weeks of treatment, which may have limited the treatment effect.

Identical approaches, with comparisons to the same historical cohort, were used to investigate associations between infliximab use and adalimumab use and the progression of spinal damage in AS [17, 18]. Of 201 patients enrolled in a controlled trial of infliximab 5 milligrams per kilogram every six weeks, data on radiographs at 96 weeks were analyzed for 156 patients (77%) who completed the open-label extension period. For adalimumab, 307 patients who participated in one of two controlled trials and who had received at least 78 weeks of treatment at 40 milligrams every other week were analyzed. The adalimumab analysis reported 85% power to detect a 1-point mSASSS difference between groups, with an estimated increase in the comparison group of 1.2 mSASSS points. The duration of AS in patients in both studies averaged 10 to 11 years, and the mSASSS at baseline ranged from 17 to 20. Mean change in mSASSS for infliximab-treated patients and adalimumab-treated patients did not differ from those of the historical cohort. In both studies, only one-third of patients had at least a 1-point increase in mSASSS over 96 weeks.

Recently a long-term extension of a placebo-controlled randomized trial of golimumab reported radiographic changes over 4 years [19]. Mean mSASSS increased by 1.6 points in those treated with golimumab 50 milligrams monthly, and by 2.0 points in those treated with golimumab 100 milligrams monthly. Placebo comparisons were not possible because placebo was given for a maximum of 24 weeks, and with escape at 16 weeks for those not having an adequate clinical response. Definite progression, defined by the authors as an increase of > 2 mSASSS points over 4 years, was observed in 28.7% of patients. Of note, mSASSS was stable in the subset of patients without syndesmophytes at baseline. While the long-term follow-up is a strength, the absence of an untreated comparison group limits the conclusions that can be drawn from this study.

OBSERVATIONAL STUDIES OF TNFi

Because prolonged use of placebos is unethical for symptomatic conditions with known effective treatments, studies of radiographic progression in AS have needed to rely on observational studies. Given the slow rate of progression in AS, investigators questioned if the null results from open-label extension studies with 2 years of observation were due to insufficient lengths of treatment. Longer observation periods might demonstrate effects not seen in the relatively short-term clinical trial extensions. In a recent study, Baraliakos and colleagues compared changes in mSASSS over 8 years between 22 patients with AS treated continuously with infliximab and 34 historical controls not treated with TNFi [20*]. Patients were selected from a somewhat larger group, based on the availability of serial radiographs. As expected, the infliximab –treated group had more active AS, but groups had similar mSASSS at baseline. The mSASSS increased similarly in both groups over the first 4 years, but diverged on the last evaluation at 8 years, with a larger increase in the untreated group. Mean overall rates were 0.9 mSASSS points per year in the treated group and 1.5 points per year in the untreated group ($p = .13$), although progression was significantly lower in the treated group from year 4 to year 8. New syndesmophyte formation was also lower in the treated group. Although the higher AS activity might favor more radiographic progression in

the treatment group, this was not observed. However, the diversity of factors associated with starting (and avoiding) TNFi make firm inferences difficult. The selection for continued treatment and/or continued observation over 8 years is also an important potential bias. A useful comparison might have been with patients who started but discontinued TNFi.

Another prospective cohort study by Haroon and colleagues recently reported associations between TNFi use and progression of mSASSS (defined as an increase ≥ 1 point per year) in a cohort of 334 patients who had paired radiographs taken at least 1.5 years apart [21*]. The mean interval between radiographs was 2.8 years and the maximum interval was 6.3 years. Sixty percent of patients were treated with TNFi, and these patients had a lower odds of mSASSS progression (adjusted odds ratio = 0.47; 95% confidence interval 0.24, 0.94) than those not treated with TNFi. Lower risk of progression was also found in an analysis that adjusted for propensity to have been prescribed TNFi. The association was stronger among patients with at least 4 years between radiographs. Risks were also lower among those treated for a greater proportion of their disease course, and for those with a shorter lag in treatment initiation after symptom onset. These results suggest that persistence and latency of treatment with TNFi, as well as a longer period of observation, influences associations with radiographic progression. As noted above, selection bias based on continued treatment and observation and unmeasured confounding potentially complicate this study as well.

STUDIES OF CONTINOUS VERSUS ON-DEMAND NSAIDS

Despite an early study suggesting that continuous use of phenylbutazone was associated with less radiographic progression [28], the question of whether NSAIDs may impact spinal damage in AS was re-examined only recently. In a 2-year open-label randomized clinical trial, 111 patients were randomly allocated to continuous treatment with celecoxib 100 mg twice daily and 101 patients were allocated to treatment with celecoxib 100 mg twice daily taken per discretion of patients for severe symptoms [22]. Of 150 patients with radiographs at baseline and 2 years, the proportion with radiographic progression (defined as > 0 mSASSS point) was lower in the continuous NSAID group (N = 76) compared with the on-demand group (N = 74) (45% vs. 22%). The mean change scores were 0.4 ± 1.7 in the continuous group and 1.5 ± 2.5 in the on-demand group (P = 0.002). Findings were unchanged using two different imputation strategies to account for missing data. Although based on a well-designed trial, the magnitude of the difference was surprising, especially considering that the difference in mean daily dose of celecoxib between the groups was only 42 mg. The mechanisms by which such a small medication difference could have resulted in the observed differences in radiographic progression were not explored. The intensity and duration of NSAID use in the on-demand group were not reported, and may have contributed to the effects seen. However, the unblinded design may have also contributed to differential use of co-interventions, such as exercise, that might have mediated part of the effect..

A recent retrospective observational cohort study examined the treatment effect of high intensity versus low intensity NSAIDs on radiographic progression [23*]. An index of NSAID use, based on mean dose and duration, was created. Among 88 patients with AS, those with high intensity NSAID use (N = 24), compared to those with low NSAID use (N =

64), were less likely to have radiographic progression (defined as mSASSS change ≥ 2 units) at 2 years of follow-up (odds ratio = 0.15, 95% confidence interval of 0.02 to 0.96, P = .045). Limitations of the study were the small sample size as well as potential selection bias. A similar NSAID index was not associated with differences in radiographic progression in the study by Haroon [21].

CONCLUSION

Contrary to previous analyses based on data from clinical trials, results from recent retrospective and prospective studies have suggested that TNFi may reduce radiographic progression in AS. The association with TNFi use was most evident with prolonged treatment, often greater than 4 years, raising the possibility that the 2 year time frame used in the extensions of clinical trials was too short to observe the association. The slow development of radiographic changes in AS complicates studies of potential disease-modifying treatments, and the radiographic measures used as endpoints are poorly sensitive to change. Given that controlled trials of several years duration are not feasible, we will need to continue to rely on carefully designed observational studies to examine the effects of treatments on the progression of spinal damage in AS. These studies should be large enough to capture patients with different medication histories, and should adjust to the greatest extent possible for biases in treatment selection. Advances that might make controlled trials of this question feasible are identification and study of patients at high risk for progression, development of a more sensitive measure of spinal damage, and identification of surrogate markers for spinal fusion. Studies to identify predictors of spinal damage are proceeding, and new measures such as those based on quantitative computed tomography may prove useful in detecting small changes in syndesmophyte size [29].

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KEY POINTS

- Analysis of data from extensions of clinical trials of TNFi have not demonstrated an effect of these medications on progression of spinal damage in AS.
- Recent long-term observational studies suggest a possible effect of TNFi on spinal damage after prolonged use.
- Data on whether NSAIDs slow the development of radiographic damage in AS are limited and conflicting.

Table 1

Studies of the association between treatment with tumor necrosis factor-alpha inhibitors (TNFi) and nonsteroidal anti-inflammatory drugs (NSAIDs) and progression of radiographic spinal damage in ankylosing spondylitis by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)

Reference	Treatment	Comparison	Number in treated group	Number in comparison group	Duration of follow-up	Mean (± SD) change in mSASSS in treated group	Mean (± SD) change in mSASSS in comparison group	P	Odds of progression (OR, 95% CI)	Proportion (%) with progression in treated group	Proportion (%) with progression in comparison group	Definition of progression (Increase in mSASSS units)
Open-label extensions of controlled trials of TNFi												
16	Etanercept	TNFi naïve Historical	257	175	Up to 2 years	0.91 ± 2.4	0.95 ± 3.2	1.00	-	-	-	-
17	Infliximab	TNFi naïve Historical	156	192	Up to 2 years	0.9 ± 2.6	1.0 ± 3.2	0.55	-	19.9	17.6	≥ 2
18	Adalimumab	TNFi naïve Historical	307	169	Up to 2 years	0.8 ± 2.6	0.9 ± 3.3	0.78	-	-	-	-
19	Golimumab	None	299	-	Up to 4 years	-	-	-	-	27.8	-	> 2
Observational studies of TNFi												
20	Infliximab	TNFi naïve Historical	22	34	8 years	0.9 ± 0.8 *	1.5 ± 1.4 *	0.13	-	-	-	-
21	Any TNFi	TNFi non-users	201	133	Up to 6.3 years	-	-	-	0.52 (0.30 – 0.88)	27	35	≥ 1 *
Randomized clinical trial of NSAIDs												
22	Celecoxib daily	Celecoxib as needed	76	74	2 years	0.4 ± 1.7	1.5 ± 2.5	0.002	-	11	23	≥ 3
Observational study of NSAIDs												
23	NSAIDs High intensive	NSAIDs Low intensive	64	24	2 years	-	-	-	0.15 (0.02 – 0.96)	8.3	21.9	≥ 2

* Change per year