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The Impact of TNF-inhibitors on radiographic progression in Ankylosing Spondylitis

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Abstract

Introduction—We studied the effect of Tumor Necrosis Factor-Alpha (TNF)-inhibitors on progressive spine damage in Ankylosing Spondylitis (AS) patients.

Methods—All AS patients (satisfying the modified New York criteria) prospectively followed and with at least two sets of spinal radiographs at a minimum gap of 1.5 years were included (n=334). Patients received clinical standard of care, which included non-steroidal anti-inflammatory drugs and TNF-inhibitors. Radiographic severity was assessed by the modified Stokes Ankylosing Spondylitis Spine Score (mSASSS). Patients with a rate of progression more than 1 mSASSS unit/year were considered progressors. Univariable and multivariable regression analyses were done. Propensity score matching (PSM) and sensitivity analysis were performed. A zero-inflated negative binomial (ZINB) model was used to analyze the effect of TNF-inhibitor on change in mSASSS with varying follow-up periods. Potential confounders like Bath AS Disease Activity Index (BASDAI), ESR, CRP, HLA-B27, gender, age of onset, smoking and baseline damage were included in the model.

Results—TNF-inhibitor treatment was associated with a 50% reduction in the odds of progression (OR: 0.52; CI: 0.30-0.88; p=0.02). Patients with a delay in starting therapy of more than 10 years were more likely to progress compared to those who started earlier (OR=2.4; 95% CI: 1.09-5.3; p=0.03). In the ZINB model TNF-inhibitor use significantly reduced progression

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when the gap between x-rays was more than 3.9 years. The protective effect of TNF-inhibitors was stronger after propensity score matching.

Conclusions—TNF-inhibitors appear to reduce radiographic progression in AS, especially with early initiation and longer duration of follow up.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory arthritis affecting the sacroiliac joints and spine associated with new bone formation and spinal fusion. Patients with AS suffer from significant pain and loss of function with associated work disability [1]. The introduction of Tumor Necrosis Factor Alpha (TNF)-inhibitors has significantly altered the landscape of treatment in inflammatory arthritis. It has proven to be an excellent treatment modality for reducing symptoms of AS [2-5]. Unlike rheumatoid arthritis (RA), the benefits of TNF-inhibitor therapy on disease modification of AS has not been demonstrated to date.

Radiographic damage in AS is quantified by the number of bone spurs (syndesmophytes), squaring, erosions and sclerosis developing at vertebral corners. Quantified radiographic damage has been shown to correlate well with spinal mobility and overall physical function [6-9]. Unlike rheumatoid arthritis and psoriatic arthritis, where TNF-inhibitors have demonstrated significant effect on progression of structural damage, the evidence to date is that the radiographic progression of AS is unaltered with the use of these agents [10-13]. The only therapy showing promise for a disease modifying effect has been sustained use of non-steroidal anti-inflammatory drugs (NSAIDs) [14].

The impact of TNF-inhibitors on radiographic progression in AS has been difficult to resolve, in part because of the relatively slow tempo of radiographic change in AS, and the hurdles this imposes on longer-term placebo-controlled trials. Despite symptomatic improvement, 3 randomized controlled trials of TNF-inhibitors could not show significant benefit on structural progression when compared with historical controls. Prospective longitudinal cohorts can provide useful information in clinical settings in which longer periods of placebo treatment arms would not be feasible or ethically defensible. We studied the effect of TNF-inhibitors on radiographic progression in a well-characterized AS patient population enrolled in a protocol-based longitudinal study.

Methods

Patients

A prospective study of patients with AS satisfying the modified New York criteria included spinal radiographs every two years to assess structural progression. From this cohort, all patients having at least two sets of radiographs were included in this analysis. Three-hundred-and-thirty-four patients were included after excluding patients with total spinal ankylosis at baseline, as progression of disease cannot be assessed in this group. A comprehensive clinical evaluation and laboratory assessment was done on scheduled visits, at least once a year, using a standardized protocol.

Disease activity at baseline was assessed by a validated patient reported index, the Bath AS Disease Activity Index (BASDAI) as well as by erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). In addition to these inflammatory markers, the following demographic variables were considered potential confounders in the model predicting progression of spine damage: age, age of onset of axial symptoms, duration of disease, HLA-B27 status, gender and smoking burden assessed by pack-year history. Radiographic disease severity in AS was assessed by a validated X-ray scoring method outlined below.

Radiographic scoring

Paired cervical and lumbar spine radiographs were available on all patients at a minimum interval of 1.5 years (mean 2.87±1.17 years; range 1.5 to 9 years). Independently one reader in USA (Reader 1) and two readers in Canada (Readers 2 and 3) scored the first and last available radiographs for each patient. All readers were blinded to the clinical details of the patient. The modified Stokes Ankylosing Spondylitis Spine Score (mSASSS) was used for scoring radiographic severity [15]. Due to the unreliability of cervical spine squaring, this element was not scored in the radiographs [16]. A change of 2 mSASSS units in 2 years (rate ≥ 1 unit/year) was defined as significant progression in AS and all patients who satisfied this criteria were labelled progressors [17,18]. For this analysis, missing mSASSS corners were not considered for calculating progression as this could lead to false values from assigning average scores to these corners.

For quantifying reliability of radiographic scoring, we calculated the intra-class correlation coefficient (ICC) for status scores (one time point) and change scores. For this analysis, the three readers who were involved in mSASSS scoring read 30-paired radiographs. The readers were blinded to the sequence of films. The scores were analyzed using analysis of variance (ANOVA) statistics and the two-way mixed absolute agreement model with single measure estimate. ICC values for agreement are rated as poor (0.00–0.40), fair to good (0.40–0.75), and excellent (>0.75) [19]. The ICC of status score for reader pairs 1 and 2 was 0.98 (95% C.I. 0.97 – 0.99; $p < 1 \times 10^{-3}$), for 1 and 3 was 0.97 (0.95-0.98) and for readers 2 and 3 it was 0.99 (0.98-0.99). The ICC of change scores for reader pairs 1 and 2 was 0.58 (95% C.I. 0.34 – 0.76; $p < 1 \times 10^{-3}$), for 1 and 3 was 0.64 (0.41-0.79) and for readers 2 and 3 it was 0.79 (0.63-0.88).

Treatment parameters

An NSAID index was calculated according to Assessment of SpondyloArthritis international Society (ASAS) recommendations [20]. Patients taking the full, recommended dose of the respective NSAID for the entire period between radiographs receive a score of 100. Those not taking NSAIDs got a score of 0. Patients with varying NSAID use were given an average NSAID index for the entire period of follow up. An NSAID index of 50 was used as a cut off point to identify patients as high and low NSAID users as done previously [21].

TNF-inhibitors were assessed as a dichotomous variable initially. Patients who were exposed to these therapies were compared to biologic-naïve patients. TNF-inhibitor exposure was quantified as the duration of therapy and the proportion of disease duration (defined as the time since onset of axial symptoms) for which the patient was receiving the drug. Patients who were on TNF-inhibitors for more than 50% of their disease duration were considered sustained users. Delay in starting biologics was calculated as the time interval between the onset of AS symptoms and the start date of the TNF-inhibitor. If the first radiograph available was performed after starting therapy, the time on therapy before the first radiograph set was calculated.

Statistical Analysis

Student t-test, Chi-square test and logistic regression model were performed where applicable. For the multivariable analysis (MVA), variables were selected from those that were significant in the univariable analysis in addition to other potential confounders. In the MVA, exposure to TNF-inhibitors (yes/no) was used in the initial model followed by related variables such as duration and delay in starting therapy. As this was an observational study, the patients were not randomized to the treatment arm. Factors that could affect the decision to treat with TNF-inhibitors was addressed by doing a sub-analysis on a select group of patients who could be matched one to one in the two arms based on the propensity to receive

the drug. To compare patients with the same propensity of being treated by a TNF-inhibitor, propensity score matching (PSM) was performed and an additional analysis was performed on the post-matched sample. As baseline BASDAI is one of the accepted criterion for initiating TNF-inhibitor therapy, PSM was done with baseline BASDAI as a predictor of receiving treatment with a caliper of 0.1. The standardized difference in BASDAI was 0.04 after matching. For tighter matching, a separate propensity matching was performed with a caliper of 0.05 and the following extended number of variables: gender, HLA-B27, baseline BASDAI, baseline ESR, baseline mSASSS, NSAID index, disease duration, baseline smoking pack-years, age of onset of symptoms. The standardized mean difference of all variables in the extended model post-matching was below 10% for all variables except HLA-B27 where the standardized mean difference was 0.11 **(Supplementary-Table-1)**. The distribution of propensity scores post-matching was similar in the TNF-inhibitor exposed and unexposed groups **(Supplementary-Figure-1)**. UVA and MVA analyses were performed as before in the post-matched samples.

Unmeasured confounders could still influence the results of observational studies and to evaluate how such an unmeasured potential confounder could affect the findings, we performed a sensitivity analysis. The sensitivity analysis examines the relationship between confounder prevalence in the non-progressor and progressor groups and how strong the effect of the confounder needs to be (odds ratio of the confounder) to negate the results of the study.

Considering the possibility of duration of follow up having an effect on the results we did a separate analysis to control for this variable. Interval between X-rays was added as a covariate in the MVA. To control for possible variability in radiographic scoring the readers were added as variables separately in the MVA. A separate analysis was done looking at the outcome of progression with an alternate definition (delta mSASSS= mSASSS at last visit - mSASSS at baseline) and accounting for the gap between radiographs. Age of onset, gender, HLA-B27 and NSAID index were controlled for in this analysis in addition to the baseline values for mSASSS, ESR, BASDAI and smoking (pack-years). More than 55% of patients in the cohort did not show any progression over the period of follow up and hence a Zero-Inflated Negative Binomial (ZINB) model was conducted to account for a significant proportion of zero values in over-dispersed delta mSASSS.

Statistical analyses were done using PASW 21, *MatchIt* package in R (version 2.14.2) and SAS 9.3 (SAS Institute Inc, Cary, NC). The respective institutional ethics boards approved the study and patients' informed consents were obtained.

Results

The mean age of patients was 40.7 ± 13.8 years. In the AS cohort 76.7% were males and 83.4% were HLA-B27 positive. The mean disease duration was 16.4 ± 12.8 years and the mean age of onset of AS was 24.2±9.9 years. The mean baseline CRP was 1.48±1.96 mg/L and the mean ESR was 17.7±19.5mm per hour. The mean baseline mSASSS score was 9.6±14.5. No baseline spinal radiographic abnormality was seen in 144 patients (43.11%) patients and 102 (30.5%) patients progressed, as defined by a change of ≥ 1 mSASSS unit/ year.

Out of 334 patients included in the study, 201 (60%) had received TNF-inhibitors for a mean duration of 2.5 ± 2.8 years. Four patients had stopped anti-TNF therapy before the baseline radiographs and 93 (27.8%) had initiated therapy before the baseline radiographs for a mean duration of 1.0 ± 1.8 years. Patients treated with TNF-inhibitors, as expected, had a higher BASDAI at baseline (**Table 1**). All other characteristics were similar between the

groups, except for a higher percentage of males in the TNF-inhibitor treated group (**Table 1**). The mean delay in starting therapy after onset of disease was 15.2 ± 11.3 years, and 60% of those on therapy (N=120) had a delay of more than 10 years from disease onset to the initiation of therapy.

Baseline radiographic damage and radiographic progression

In the univariable logistic regression **(Table 2)**, baseline radiographic damage (defined as the baseline mSASSS) was associated with progression (OR=1.07; 95% CI= 1.05-1.09; p<0.001). The rate of progression of the mSASSS scores was higher in males than females (1.2±1.9 vs 0.7±1.7 mSASSS unit/year; p=0.04). However, after controlling for baseline mSASSS, gender was not associated with progression significantly **(Table 2)**. Similarly, age of onset of axial symptoms, duration of disease, HLA-B27 status and baseline BASDAI were not associated with progression after controlling for baseline mSASSS **(Table 2)**.

Relationship of baseline inflammatory markers to radiographic progression

Baseline values of ESR (OR=1.02; 95% CI=1.01-1.04; p<0.001) and CRP (OR=1.02; 95% CI=1.00-1.04; p=0.03) were associated with progression after controlling for baseline radiographic damage. Baseline ESR is more generalizable across different sites and used in the multivariable models of progression as a potential confounder. As CRP testing was done separately in the different centers, the values were standardized for all patients enrolled and retested. The standardized baseline CRP (ZCRP) remained a significant factor associated with radiographic progression (OR=1.59; 95% CI=1.24-2.03; p<0.001).

Smoking and radiographic progression

In the entire cohort 61.1% (N=204) had never smoked while 13.5% (N=45) had smoked more than 10 pack-years. In the univariable analysis, smokers were more likely to progress (OR=1.7; 95% CI = 1.1-2.8; p=0.02). The rate of mSASSS progression increased with increasing pack-years of smoking with the highest rate seen in smokers with more than a 10 pack-year history **(Figure 1)**. Compared to those patients who smoked less, patients who smoked more than 10 pack-years had a significantly higher rate of progression (1.9 ± 2.0 vs 0.9 ± 1.9, p=0.005). In the univariable model, smoking pack-years was significantly associated with progression (OR=1.06; 95% CI=1.02-1.09; p=0.002).

Non-steroidal anti-inflammatory drugs and radiographic progression

The NSAID index was calculated as described above. There was significant variability in the intake of NSAIDs and the mean index was 35.36 ± 37.51. Twenty seven percent of patients had not taken NSAIDs during the observation period. A total of 117 (35%) had an NSAID index of above 50 and were considered high users. The NSAID index was not associated with radiographic progression. There was no significant difference in the rate of progression between high or low NSAID users.

TNF-inhibitors and radiographic progression

After correcting for the baseline mSASSS, those who had received TNF-inhibitors had a 50% reduction in odds of progression compared to those who had not been on TNF-inhibitors (OR: 0.52; CI: 0.30-0.88; p=0.02). The total duration of treatment was inversely associated with progression (OR=0.90; CI: 0.82-0.99; p=0.04). The duration of treatment expressed as a percentage of total disease duration was significantly associated with radiographic progression after adjusting for baseline mSASSS. Patients who were on biologics for more than 50% of their disease duration had lower odds of progression (OR=0.2 95% CI: 0.04-0.92; p=0.04) compared to patients who were not. Patients who were

not on TNF-inhibitors for the greater part of their disease duration had increasingly higher rates of mSASSS progression (**Figure 2A**).

In the patients who were on TNF-inhibitors, the rate of mSASSS progression increased with an increasing delay in starting treatment (**Figure 2B**). In the regression analysis after correcting for the baseline mSASSS, patients with a delay in starting therapy of more than 10 years were more likely to progress compared to those who started earlier (OR=2.4; 95% CI: 1.09-5.3; p=0.03). There was a significant impact observed when the probability plots of patients who received TNF-inhibitors within 10 years of symptom onset were compared to those who started treatment later (**Figure 2C**). Thus not only the use of TNF-inhibitors but also the total duration and delay in starting therapy were important in determining the rate of mSASSS progression.

Independent factors associated with radiographic progression

Stringent MVA was done with multiple models **(Table 2)**. In the final model, we adjusted for variables that were considered as potential confounders. Significant variables in the final model included baseline mSASSS baseline ESR, smoking pack-year history, and TNF-inhibitors (**Table 2**). In the final model multivariable model, TNF-inhibitor use was significantly associated with more than 50% reduction in the adjusted odds of progression (Adj. OR: 0.47; 95% CI: 0.24-0.94; p=0.03).

Sensitivity analysis was used to evaluate the magnitude of any unknown confounders on measures of associations reported in this study. The sensitivity analysis **(Supplementary-Figure-2)**, examines the relationship between prevalence of confounders in the non-progressor and progressor groups and the odds ratio of the confounders with respect to TNF-inhibitor use. For example, if the prevalence of an unmeasured confounder in the non-progressor group was 30% and 5% in the progressor group (green line), the odds ratio of the confounder would need to be about 6.5 or higher to account for the significant differences observed in TNF-inhibitor use. So the odds ratio of the confounder required to nullify the observed differences in TNF-inhibitor use is more than 6.5.

Propensity score matching to confirm the effect of TNF-inhibitors on radiographic progression

A total of 142 patients could be included in the post-match analysis after PSM with the extended variables described in the methods. A separate PSM with BASDAI alone including 194 patients was performed. Univariable followed by multivariable logistic regression analysis in the post-match samples were done **(Table 3)**. The final multivariable model here included smoking (in pack-years), gender, age of onset, TNF-inhibitor use and baseline values of mSASSS and ESR. As disease duration was strongly correlated with baseline mSASSS in the post match cohort (R=0.52; p<0.001), disease duration was not included in the complete model. However, neither inclusion of disease duration in the complete model nor other potential confounders in the final model influenced the association between use of TNF-inhibitors and progression.

TNF-inhibitor use was associated with a 70% reduction in odds of progression in the MVA model (OR: 0.30; 95% CI: 0.11-0.78; p=0.01). Smoking and baseline mSASSS were also significantly associated with progression. ESR at baseline was marginally significant (p=0.08) in the MVA model. Standardized CRP, used in place of ESR in MVA, was significantly associated with progression (OR= 1.6; 95% CI: 1.01-2.51; p=0.05). The use of standardized CRP in place of ESR did not have a significant effect in the MVA model. In additional PSM studies with BASDAI alone as predictor, 194 patients could be matched and

TNF-inhibitor use remained significantly associated with progression (OR: 0.43; 95%CI: 0.20-0.94; p=0.03) in the MVA.

The duration of TNF-inhibitor use, when used in the model in place of the dichotomous variable 'TNF-inhibitor use', was inversely associated with progression (OR=0.84; 95% CI: 0.73-0.96; p=0.01) after adjusting for baseline radiographic damage, ESR, smoking (in pack-years), gender and age of onset. Except for 3 patients, all TNF-inhibitor treated patients had at least 1 year of treatment between the first and last X ray. When these 3 patients were excluded from the analysis, TNF-inhibitor use remained inversely associated with progression (OR: 0.30; 95% CI: 0.11-0.82; p=0.02).

As this was not a randomized controlled trial, patients were followed for varying lengths of time. The gap between first and last x-rays scored was similar between the TNF-inhibitor user and non-user groups in terms of mean duration ± SD (2.9±1.03 vs 2.8±1.1 years) and range (1.5-5.5 vs 1.6-6.3 years). The results remained significant after adjusting for the duration of follow up in the MVA model with the odds of progression on TNF-inhibitors being 0.29 (95% CI 0.11-0.79; p=0.01). In the zero inflated negative binomial model (**Figure 3**) when the gap between X-rays increased above 3.9 years, TNF-inhibitor use was significantly associated with a lower delta mSASSS (Relative Ratio (RR)=0.42, 95% CI= [0.18, 0.98], p=0.04). There was no significant difference between the groups when the gap between radiographs was less than 3.9 years.

Discussion

This is the first study to show a clear association between the use of TNF-inhibitors and progression of damage in AS. Both the duration of therapy and the timing of treatment initiation are important in the ultimate effect on the rate of damage in the spine of AS patients. The long duration of follow-up and large number of patients and controls in this study have contributed to its strength. The comparison with a control group of AS patients, not receiving TNF-inhibitors, from the same cohorts and followed concurrently in a real world setting was a noteworthy advantage. The large number of patients in our cohort allowed us to do PSM. This is an important aspect of the study as PSM reduces bias in the selection of patients in observational studies. Thus patients in the two groups had equal propensity to receive TNF-inhibitors. An additional sensitivity analysis indicates that unobserved confounders have to be very strong to negate the findings of this study, suggesting our observations are true with a very high likelihood. Previous studies examining the effect of TNF-inhibitors on patients included in randomized controlled trials were followed for shorter duration and the comparison group was a historical cohort [10-12].

An important observation arising from this study is the therapeutic advantage of both early intervention with TNF-inhibitors and of total duration of treatment. Prior studies that attempted to demonstrate disease-modifying effects of TNF-inhibitors were hampered by the structure of the randomized controlled trials, which included patients with longstanding disease, and short observation periods. More than 40% of our AS patients on biologics had started TNF-inhibitor therapy with less than 10 years of disease duration, which is a different profile from many other reports of biologics in AS, and this could have influenced our results. Any effect of duration of follow-up has been minimized in an additional MVA model controlling for gap between X-rays. Moreover in the post-matched sample the duration of follow-up was essentially identical in the two cohorts. In an additional analysis, patients were grouped based on the gap between x rays and a different dependent variable for progression (delta mSASSS) was used. This analysis showed a significant effect of TNF-inhibitors in reducing the progression of mSASSS with longer follow up.

We have shown the effect of smoking on radiographic progression independent of baseline inflammation, damage and the use of TNF-inhibitors. This is the first study in Ankylosing Spondylitis to show a strong effect of level of smoking on progression. Several studies have shown that AS patients who smoke have worse functional outcomes and greater radiographic severity[22-25]. In early disease cohorts, smoking has recently been assessed. In the Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort smokers had more inflammation on MRI in both the sacroiliac joints and spine in addition to more structural damage by the mSASSS [26]. In the German Spondyloarthritis Inception Cohort (GESPIC), smoking was significantly associated with radiographic progression at 2 years in patients with axial spondyloarthritis or AS with disease duration ≤ 10 years [17]. None of these patients were exposed to TNF-inhibitors.

It is not surprising that we did not find baseline demographic factors that significantly modify the risk of progression of structural damage. Several studies looking at candidate predictors of mSASSS progression have not identified baseline demographic features, including HLA-B27 and gender [17,18,27]. The strong effect of baseline radiographic severity likely negates other minor effects. In a recent study, when baseline radiographic severity was not included in the MVA, gender and age were important predictors of progression [28]. An earlier cross-sectional study from our cohort assessed gender differences in AS [29]. In patients with long standing AS, radiographic severity (assessed by Bath Ankylosing Spondylitis Radiographic Index [BASRI]) was significantly worse in males. Baraliakos et al found no gender effect on mSASSS progression among 146 AS patients [27]. They did report that rapid progressors were more likely to be males, however this was not controlled for baseline radiographic severity. A more recent study of radiographic progression in axial spondyloarthritis showed only a trend to more progression in men compared to women [17].

NSAIDs have been proposed to be disease modifying in AS [21,30,31]. Two studies and one re-analysis of the data have reported this finding. We have not been able to show the same effect, though these are not similar cohorts or study designs. There was a suggestion that NSAIDs are effective when used continuously in patients who had higher baseline inflammation and more radiographic damage. We could not demonstrate any effect of NSAID therapy after correcting for baseline CRP or ESR values. There was no difference in the high NSAID index (>50/100) patients when compared to those with low NSAID index (<50/100). There was no effect when the biologic-naïve and TNF-inhibitor user groups were tested separately. Despite controlling for several potential confounding factors and after multiple analyses, we did not see a disease modifying effect of NSAIDs on radiographic progression in AS.

The limitations of this study include potential unmeasured confounders and potential biases that cannot be adjusted for, as this was not a randomized controlled trial. In this study, TNF-inhibitors were given to patients who were not well controlled on NSAIDs and had high disease activity. It is not clear if the effect on preventing radiographic progression would be present in patients who are otherwise well controlled. Hence the decision to start TNF-inhibitors should still be made based on patients' symptoms and lack of response or toxicity to NSAIDs.

Conclusions

This is the first study to show a protective effect of TNF-inhibitors on radiographic progression in AS. TNF-inhibitors are most effective when started sufficiently early in the disease course and when treatment is sustained for a longer period of time. Smoking and baseline inflammation continue to be important risks and radiographic baseline damage remains the strongest predictor of future radiographic progression in AS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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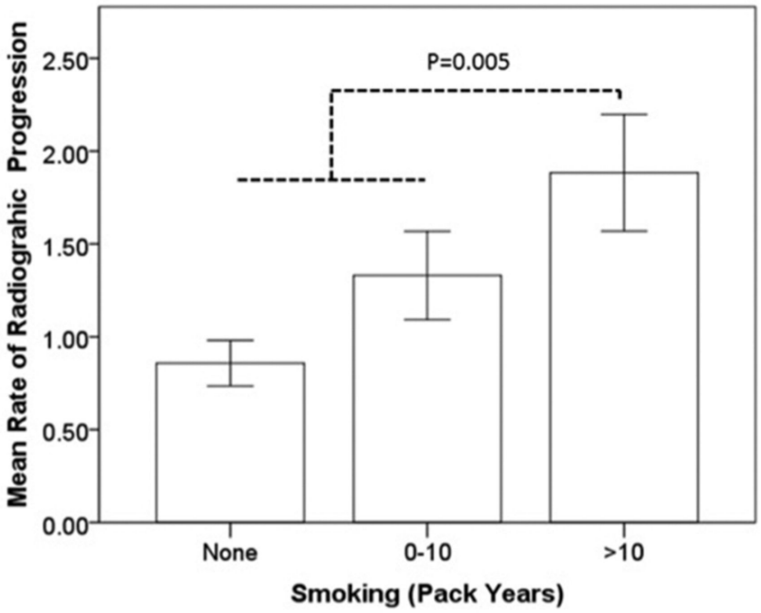

Figure 1. Smoking and Rate of Radiographic Progression

Comparison of the rate of mSASSS progression in patients who smoked compared to those who do not. The rate of progression was significantly different from the group of patients who either did not smoke or smoked less than 10 pack-years. A clear increase in progression rate is seen with increasing total burden of smoking.

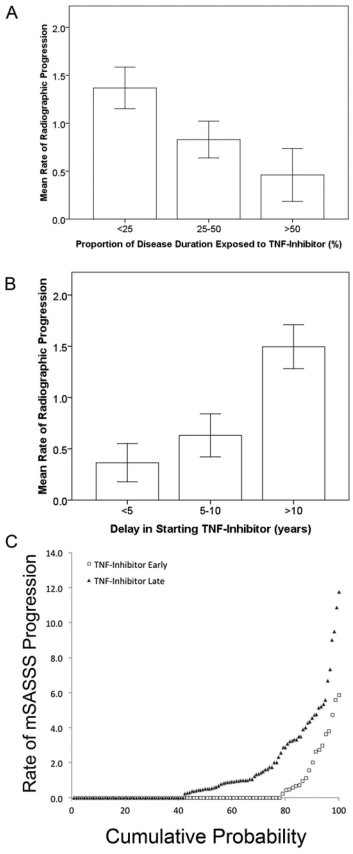

Figure 2. TNF-inhibitors and rate of radiographic progression

This shows the effect of duration and point of starting therapy among AS patients on TNF-inhibitors. (A) The duration of therapy in relation to the total duration of disease is plotted against the rate of progression. As patients remained on therapy for a greater proportion of their disease duration, the rate of radiographic progression decreased. There was a significant difference in the rate of progression in those patients who remained on the drug for more than 50% of their disease duration compared to others. (B) The delay in starting TNF-inhibitors was significant in determining the effect it had on the rate of progression of radiographic damage. The earlier the therapy was initiated, the better the results. (C) Cumulative probability plots show a striking difference in radiographic progression, with patients who got TNF-inhibitors within 10 years of onset of disease progressing at a much slower rate compared to those who received the drug after 10 years.

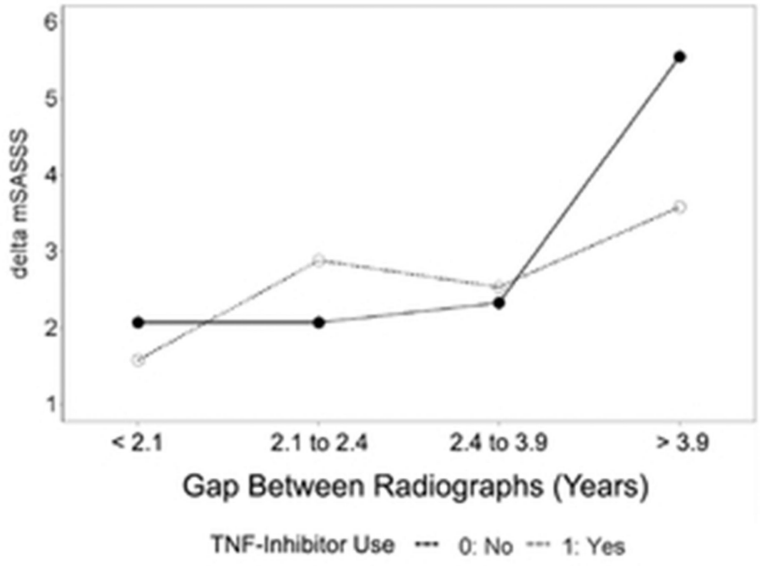

Figure 3. Zero-Inflated Negative Binomial Model for change in mSASSS scores over time

There were several patients who did not progress during the follow up period. Zero- inflated negative binomial model is conducted to account for many portions of zeros (55.4%) in over dispersed delta mSASSS. TNF-Inhibitor use was significantly associated with less progression (defined by change in mSASSS), when patients were followed up for more than 3.9 years. There was no significant difference between two groups during early time period. The expected decrease of delta mSASSS in the TNF-inhibitor user group compared to non-user group was 58% (Relative Ratio (RR)=0.42, 95% CI= [0.18, 0.98], p=0.044).

Table 1

Baseline Variables in TNF-inhibitor users and non-users (naïve patients)

Variable	TNF-inhibitor Naïve (N=133)	TNF-inhibitor Treated (N=201)	p value
Age (yrs)	42.50±14.6	39.43±13.2	ns
Female (%)	32.33	17.41	0.002
HLA-B27 (%)	84.96	82.41	ns
Disease Duration (yrs)	16.38±14.4	16.47±11.8	ns
Baseline mSASSS	8.20±13.8	10.60±14.9	ns
Smoking (pack-yrs)	3.34±8.3	3.87±8.0	ns
ESR (baseline)	17.02±17.3	18.11±20.9	ns
CRP (baseline)	1.69±1.9	1.33±2.0	ns
BASDAI (baseline)	3.61±2.4	4.64±2.5	0.001

ns indicates p-value > 0.05

Table 2

Regression analysis in the full cohort (N=334) to identify factors associated with progression

Variable	Odds Ratio	95% CI		p value (UVA)	p value (MVA: All Variables)
		Lower	Upper		
Baseline mSASSS	1.07	1.05	1.09	**<0.001**	**<0.001**
Baseline ESR (mm/Hr)	1.02	1.01	1.04	**<0.001**	**0.005**
Baseline BASDAI	1.10	0.98	1.2	0.09	0.15
Smoking (Pack Years)	1.06	1.02	1.09	**0.002**	**0.03**
Male vs Female	1.52	0.78	2.97	0.22	0.25
Age of onset	1.02	0.99	1.05	0.07	**0.02**
Disease duration	1.01	0.99	1.03	0.26	0.08
HLA-B27	1.08	0.54	2-17	0.82	0.58
TNF-inhibitor use	0.52	0.30	0.88	**0.02**	**0.03**
NSAID-index	1.01	0.99	1.01	0.15	0.71
Multivariable Analysis including only variables significant in the univariable analysis[#]					
Baseline mSASSS	1.06	1.04	1.08	**<0.001**	
Baseline ESR (mm/Hr)	1.02	1.01	1.04	**0.004**	
Baseline BASDAI	1.10	0.95	1.25	0.09	
Smoking (Pack Years)	1.05	1.01	1.09	**0.009**	
Age of onset	1.03	0.99	1.06	0.07	
TNF-inhibitor use	0.47	0.24	0.94	**0.03**	

UVA: Univariate Analysis; MVA: Multivariable Analysis; CI: Confidence Interval

[#]In the restricted MVA model only those variables that were significant in the UVA at p≤0.1 were included.

Table 3

Logistic Regression Analysis in the post-matched samples (N=142, Extended Model PS)

Variable	Odds Ratio	95% CI		p value (UVA)	p value (MVA: All Variables)
		Lower	Upper		
Baseline mSASSS	1.05	1.03	1.08	**<0.001**	**0.002**
Baseline ESR (mm/Hr)	1.02	0.99	1.04	0.06	0.07
Baseline BASDAI	1.06	0.90	1.24	0.51	0.71
Smoking (Pack Years)	1.1	1.03	1.15	**0.005**	**0.01**
Male vs Female	2.01	0.72	5.7	0.18	0.21
Age of onset	1.03	0.99	1.07	0.12	0.50
Disease duration	1.02	0.98	1.05	0.32	NI*
HLA-B27	0.64	0.23	1.77	0.39	0.44
TNF-inhibitor use	0.38	0.16	0.89	**0.03**	**0.01**
NSAID-index	1.01	0.99	1.02	0.35	0.53
Multivariable Analysis including only variables significant in the univariate analysis*					
Baseline mSASSS	1.05	1.02	1.08	**0.001**	
Baseline ESR (mm/Hr)	1.02	0.99	1.05	0.08	
Male vs Female	2.3	0.75	6.98	0.15	
Smoking (Pack Years)	1.09	1.02	1.17	**0.01**	
Age of onset	1.02	0.98	1.07	0.37	
TNF-inhibitor use	0.30	0.11	0.78	**0.01**	

UVA: Univariate Analysis; MVA: Multivariable Analysis; CI: Confidence Interval NI: Not included (Disease duration was strongly correlated with baseline mSASSS in the post-match cohort and was not included in the MVA. Inclusion of disease duration in the MVA did not however affect the level of significance of TNF-inhibitor use).

*Restricted model includes variables that were significant in the univariate analysis with p value ≤ 0.2. After including only variables significant at p ≤ 0.1, TNF-inhibitor use remained strongly associated with less progression (not shown).