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ORIGINAL RESEARCH

Sacroiliac joint radiographic progression in axial spondyloarthritis is retarded by the therapeutic use of TNF inhibitors: 12-year data from the SCQM registry

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ABSTRACT

Objectives To analyse the effect of tumour necrosis factor inhibitors (TNFi) on sacroiliac joint (SIJ) radiographic progression in axial spondyloarthritis (axSpA).

Methods Patients with axSpA in the Swiss Clinical Quality Management cohort with up to 12 years of follow-up and radiographic assessments every 2 years were included. SIJs were scored by two readers according to the modified New York criteria blinded to chronology. The relationship between TNFi use before or during a 2-year radiographic interval and SIJ progression was investigated using generalised estimating equation models with adjustment for potential confounding. Progression was defined as worsening of ≥1 grade in ≥1 SIJ and ignoring a change from 0 to 1 over 2 years, if both readers agreed. A third reading of radiographs was integrated in sensitivity analyses.

Results A total of 515 patients with axSpA contributed to data for 894 radiographic intervals (24 progression events). In patients with complete covariate data, prior use of TNFi reduced the odds of progression (OR 0.21, 95% CI 0.07 to 0.65). A comparable effect was found for use of TNFi for ≥1 year within a 2-year radiographic interval (OR 0.21, 95% CI 0.08 to 0.55). The inhibitory impact of TNFi was confirmed if progression was demonstrated in 2/3 readings: OR 0.50, 95% CI 0.28 to 0.89 and OR 0.46, 95% CI 0.27 to 0.78 for TNFi treatment before and for ≥1 year within the interval, respectively.

Conclusion TNFi are associated with deceleration of SIJ radiographic progression in patients with axSpA if treatment is continued for ≥1 year.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

⇒ Observational studies suggest that treatment with tumour necrosis factor inhibitors (TNFi) can inhibit spinal radiographic progression in axial spondyloarthritis (axSpA).

⇒ Whether TNFi might be able to retard radiographic progression at the level of the sacroiliac joints (SIJ) remains controversial.

WHAT DOES THIS STUDY ADD?

⇒ TNFi are associated with retardation of SIJ radiographic progression in axSpA if treatment is continued for at least 1 year.

HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE OR FURTHER DEVELOPMENTS?

⇒ Confirmation of a disease-modifying effect of TNFi at both sacroiliac and spinal levels strengthens the concept of axSpA being a single disorder with several phenotypes.

⇒ As structural damage in axSpA starts in the SIJ and continues in the spine, early and continued anti-inflammatory treatment might completely abrogate both sacroiliac and spinal progression.

INTRODUCTION

Axial spondyloarthritis (axSpA) is an inflammatory rheumatic disease that primarily affects the sacroiliac joints (SIJ) and the spine.[1 2] There is increasing consensus that this disorder encompasses both non-radiographic and radiographic disease forms (nr-axSpA and r-axSpA, respectively),[3 4] depending on whether clear sacroiliac damage is already observed on conventional X-rays.[5] The latter is defined by the modified New York criteria (mNYc) for postinflammatory sacroiliac radiographic changes.[6] While some patients with nr-axSpA may never develop definite SIJ structural lesions, a significant proportion of patients will evolve from nr-axSpA to r-axSpA, although the percentage over a period of 2–5 years seems rather small.[7 8] Structural changes of the spine usually accumulate after substantial SIJ damage is established.[9] Evidence is accruing that treatment with tumour necrosis factor inhibitors (TNFi) is able to decelerate the appearance of these spinal radiographic

changes.[10] With regard to SIJs, treatment with TNFi for at least 12 months in a previous radiographic interval was associated with a lower SIJ progression in the following 2-year interval in a very recent observational study.[11] Although the significance of SIJ structural changes has been questioned from a functional point of view,[12] confirmation of an inhibition of radiographic progression not only at the level of the spine, but also of the SIJs, would strengthen the paradigm of axSpA being a single disorder.[13] The aim of the study was to investigate the relationship between treatment with TNFi and SIJ radiographic progression independently of classification status as nr-axSpA and r-axSpA in a longitudinal analysis with 2-year clinical and radiographic intervals and up to 12 years of follow-up in a large observational cohort of patients with axSpA.

METHODS

Study population

The Swiss Clinical Quality Management (SCQM) Foundation in Rheumatic Diseases is associated with the Swiss Society for Rheumatology (SGR) and runs a national registry for inflammatory rheumatic diseases (rheumatoid arthritis, axSpA, psoriatic arthritis, undifferentiated arthritis, giant cell arteritis and polymyalgia rheumatica). The online database provides an integrated feedback system to patients and treating rheumatologists to be used as a quality management tool for treatment (treat-to-target decision making) during real-life clinical practice. All rheumatologists practising in Switzerland can be affiliated with SCQM, irrespective of them working in non-academic or academic institutions (rheumatology departments of 42 hospitals, including 5 university hospitals) or in private rheumatology practices. Approximately 50% of SCQM patients are followed in private practices. Treatment recommendations by the SGR stipulate that patients with inflammatory rheumatic diseases should be seen at least once a year by a rheumatologist. This is the basis for annual SCQM visits with comprehensive physician and patient questionnaires. Shorter questionnaires including disease activity measurements and clinical manifestations are recommended for intermediate visits and particularly before and 3 months after initiation of a new treatment. The data are available in anonymised form for long-term observational studies. Patients provide informed consent at inclusion in the registry.

The ongoing axSpA cohort within SCQM was initiated in 2005.[14] Inclusion criteria include a clinical diagnosis of axSpA (ankylosing spondylitis or other forms of SpA with predominantly axial disease) by a rheumatologist, irrespective of age, disease duration and treatment. The questionnaires for rheumatologists include all parameters relevant to assess spondyloarthritis[15] and the fulfilment of the Assessment of SpondyloArthritis international Society classification criteria[3] including prior MRI positivity, disease manifestations (presence of inflammatory back pain; presence of peripheral arthritis via a 44-joint homunculus, presence of enthesitis via a homunculus reflecting the Maastricht Ankylosing Spondylitis Enthesitis Score[16] sites (modified to include the plantar fasciae), ever dactylitis), exact measurements for the Bath Ankylosing Spondylitis Mobility Index[17]), exact start and stop dates for conventional and biological disease-modifying antirheumatic drugs, treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics as yes/no; levels of C-reactive protein (CRP), erythrocyte sedimentation rate and of haemoglobin; human leucocyte antigen B27 (HLA-B27) status; smoking status; information on physical activity (number of exercise units per week). There is no information on whether NSAIDs are used on demand or continuously between visits. The patient questionnaire includes the Patient Global Assessment, the Bath Ankylosing Spondylitis Disease Activity and Functional Indices (BASDAI[18] and BASFI,[19] respectively), assessment of quality of life (EuroQol 5 domains; EQ-5D) and the Short Form 36 (SF-36) questionnaire (later changed to the SF-12) on numerical rating scales. The online database automatically calculates the Ankylosing Spondylitis Disease Activity Score (ASDAS)[20] and the patient-reported outcomes as soon as the rheumatologist and the patient fill in the respective data. The patient receives a reminder to fill in the questionnaires shortly ahead of the consultation, if the visit has been scheduled via the SCQM tool, allowing a treat-to-target treatment approach.

Given the gap in knowledge concerning radiographic progression and disease-modifying capacities of approved drugs, radiographic assessments were recommended from start of SCQM to be performed every 2 years (anterior-posterior pelvis radiograph, anterior and lateral radiograph of the lumbar spine, lateral radiograph of the cervical spine). The decision to perform radiographs remains with the rheumatologists and the patients. The radiographs are usually ordered in conjunction with an annual visit and are performed either immediately after the visit if the institution has a radiology department or an X-ray equipment or within days/weeks after the visit if the radiographs have to be performed elsewhere. Disease activity measurements were mapped to an X-ray date if available during a timeframe of ±30 days. A timeframe of 90 days before the X-ray and 30 days after the X-ray was considered for mapping other variables to a specific X-ray date. The visit closest to the X-ray was chosen if several measurements were available during the respective timeframe.

Inclusion criteria

Patients with a clinical diagnosis of axSpA in the SCQM Registry were included in the current study if they fulfilled the ASAS 2009 classification criteria and had at least 2 pelvis radiographs at an interval of 2 years±6 months, irrespective of classification status as nr-axSpA or r-axSpA.[14] We used the central reading of pelvis radiographs in the SCQM database for classification purposes and selection of patients (‘database scoring’), as it was

available to rheumatologists for treatment decisions. This reading was provided by two members of the SCQM axSpA scientific board and a third independent adjudicator as soon as a radiograph was uploaded to the database as a service to the treating rheumatologist.

Assessment of SIJ radiographic progression

All pelvis radiographs of patients fulfilling the inclusion criteria of the current study were rescored by two trained and calibrated readers (AC and RM) independently. They were blinded to all other information. The readers scored all radiographs per patient without knowing their chronological order. The scoring was performed according to the mNYc: grade 0=normal; grade 1=suspicious changes; grade 2=minimal abnormalities; grade 3=unequivocal abnormalities; and grade 4=complete ankylosis.[6] Informed by differences in the sensitivity to change of different definitions of radiographic progression at the level of the SIJ,[8 21] the following primary outcome for progression was chosen: worsening of at least one grade in at least one SIJ and ignoring a change from 0 to 1 over 2 years. It was only considered to be present if both readers agreed. We used an alternative definition of radiographic SIJ progression as a secondary outcome: a change in the total mNY score (sacroiliitis sum score (SSS)), expressed as a continuous variable from −8 to 8 (4 grades per SIJ with the outcome presented as the mean score of the 2 readers).[7 8] The potential of improvement of the SIJ score during follow-up was also evaluated (reduction of at least one grade in at least one SIJ with a baseline score of at least 2 in the improved SIJ). We decided a priori to not assess progression from nr-axSpA to r-axSpA for the following reasons: first, the rate of progression from one disease state to the other within 2 years was shown to be rather slow, a fact that might severely impede demonstration of deceleration.[7 8] Second, we have recently shown that the cut-off of SIJ scoring differentiating between nr-axSpA and r-axSpA seems suboptimal to predict clinically relevant outcomes.[22] Finally, as already mentioned, sensitivity to change of progression between disease states is much lower than for the outcome chosen.[8 21]

Progression in the main analysis was only considered if both readers agreed on the outcome to only concentrate on undoubtful images in the context of the analysis of potential inhibition of progression. In a sensitivity analysis, the 'database scoring' of pelvis radiographs (see paragraph on inclusion criteria) was integrated in the analyses as a third reading. Progression according to the binary outcome as defined above was considered if it was observed in 2/3 readings. This analysis allowed for more adequate information on the extent of the measurement error (increase in background noise with more important worsening as well as improvement in SIJ scores).

Statistical analyses

Reliability of the scoring was assessed with weighted Kappa values of the right SIJ scores and the left SIJ scores of the two readers. All kappa values were interpreted according to Landis and Koch.[23] In addition, we calculated the intraclass correlation coefficient (ICC; single unit, type agreement, two way) on the sum of the left and the right SIJ scores (SSS).

The relationship between TNFi treatment and radiographic progression over time was investigated using generalised estimating equations (GEE)[24] in patients with a baseline SSS≤7 and available covariate information. The method takes into account the issue of repeated measurements within a patient. All GEE models were fitted using an exchangeable correlation structure. Binomial GEEs were used for the main models with binary outcomes, and Gaussian GEEs were used for the models that analyse the continuous change of the SSS within the radiographic interval. The GEE models were adjusted for potential confounders and/or explanatory variables for SIJ progression: baseline damage (baseline SSS), sex, symptom duration, HLA-B27 status, smoking status, NSAID use at start of each radiographic interval (yes/no) and disease activity at start of each radiographic interval as assessed by the ASDAS.[20] ASDAS was replaced by BASDAI and CRP in a sensitivity analysis. Paralleling our analysis of the impact of TNFi on spinal radiographic progression,[24] the following variables for TNFi use were introduced in the longitudinal models: (1) use of TNFi *prior* to the radiographic interval as yes/no if still ongoing, independently of the length of use and (2) treatment with TNFi *during* the 2-year radiographic interval as <1 year versus ≥1 year of continuous treatment versus no treatment. We checked for interaction between treatment with TNFi and treatment with NSAIDs. To address the potential issue of confounding by indication, a model was built up that was adjusted for the ASDAS value before start of TNFi. The ASDAS value at inclusion in SCQM was used in this model for patients not treated with TNFi.

RESULTS

A total of 515 patients with axSpA presented with at least 2 pelvis radiographs at an interval of 2 years±6 months (894 radiographic intervals). Baseline characteristics of these patients at first radiograph are provided in table 1 (male sex 66%, HLA-B27 positivity 80%, nr-axSpA 46.2%). In comparison with all patients with axSpA in SCQM (characteristics shown in the online supplemental table S1), patients with sequential radiographs were in a higher proportion in the nonradiographic disease state, were more often treated with TNFi and had lower disease activity measures (BASDAI, ASDAS, proportion of patients with enthesitis; table 1). Mean (IQR) time between radiographs was 2.1 (1.9; 2.3) years. The scores of both readers for each SIJ for the 1470 scored X-rays (at start and end of 894 intervals of 2 years±6 months) according to the mNY scoring system[6] are provided in the online supplemental figure S1. Interobserver reliability assessed by the weighted Kappa was 'moderate' for both the right and left SIJ scores (0.49, CI 0.46 to 0.51 and 0.46,

Table 1 Baseline characteristics at first radiograph

Parameter	All patients N=515		Patients with the potential of SIJ progression (mean SSS≤7) N=415		Patients with complete data in multivariable analyses N=302	
Male sex, N (%)	515	341 (66.2)	415	258 (62.2)	302	184 (60.9)
HLA-B27 positive, N (%)	478	388 (81.2)	387	308 (79.6)	302	243 (80.5)
nr-axSpA, N (%)	515	238 (46.2)	415	238 (57.4)	302	174 (57.6)
Age, years	515	40.5 (10.9)	415	39.6 (10.6)	302	39.2 (10.6)
Symptom duration, years	512	14.2 (10.6)	414	12.4 (9.8)	302	12.8 (9.5)
BASDAI	439	4.1 (2.3)	351	4.1 (2.2)	302	4.1 (2.2)
ASDAS	410	2.7 (1.1)	328	2.7 (1.0)	302	2.6 (1.0)
CRP, mg/L	444	9.8 (14.8)	358	8.7 (13.6)	302	8.7 (14.0)
BASFI	440	2.8 (2.4)	353	2.6 (2.4)	302	2.6 (2.3)
BASMI	458	2.0 (2.0)	370	1.5 (1.6)	300	1.5 (1.5)
Current enthesitis, N (%)	463	205 (44.3)	374	172 (46.0)	297	135 (45.5)
BMI 25–30, %	465	151 (32.5)	372	120 (32.3)	283	90 (31.8)
BMI>30, %	465	74 (15.9)	372	61 (16.4)	283	46 (16.2)
On NSAID treatment, N (%)	463	364 (78.6)	376	296 (78.7)	302	235 (77.8)
On csDMARD treatment, N (%)	515	62 (12.0)	415	47 (11.3)	302	31 (10.3)
On TNFi treatment, N (%)	515	235 (45.6)	415	181 (43.6)	302	121 (40.1)
Years of TNFi treatment in treated patients	235	2.6 (2.3)	181	2.5 (2.2)	121	2.8 (2.3)
Current smokers, N (%)	466	169 (36.3)	375	136 (36.3)	302	110 (36.4)
Patients with different number of radiographic intervals*, N (%)	515		415		302	
1 interval		288 (55.9)		231 (55.7)		182 (60.3)
2 intervals		126 (24.5)		108 (26.0)		75 (24.8)
3 intervals		63 (12.2)		47 (11.3)		31 (10.3)
4 intervals		28 (5.4)		22 (5.3)		12 (4.0)
5 intervals		7 (1.4)		6 (1.4)		2 (0.7)
6 intervals		3 (0.6)		1 (0.2)		0 (0.0)

Except where indicated otherwise, values are the mean (SD).
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BMI, Body Mass Index; CRP, C-reactive protein (CRP) levels; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HLA-B27, human leucocyte antigen B27; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; nr-axSpA, nonradiographic axial spondyloarthritis (central consensus scoring in database); NSAID, non-steroidal anti-inflammatory drug; SSS, Sacroiliitis Sum Score; TNFi, tumour necrosis factor inhibitor.

CI 0.44 to 0.49, respectively). The ICC of the agreement of the SSS yielded the same level of reliability: 'moderate' (ICC 0.64, CI 0.29 to 0.79). With regard to the binary SIJ outcome after 2 years (progression/regression), worsening of at least one grade in at least one SIJ and ignoring a change from 0 to 1 over 2 years, progression was observed in 24/703 radiographic intervals (3.4%, table 2). A 2-by-2 table for progression as observed by the two readers is shown in the online supplemental table S2. It was observed in 5/377 intervals with prior TNFi use (1.3%) and in 19/326 intervals without prior TNFi use (5.8%). Regression was observed in only 1/867 intervals (0.12%).

SIJ radiographic progression over 2 years

Patients with complete bilateral SIJ ankylosis as scored by at least one reader (SSS>7, N=100) were excluded from further analyses. Baseline characteristics of the remaining patients (N=415) are depicted in table 1. Mean (±SD) change in the SSS was 0.1 (±0.4) points. A multivariable model was set up to identify factors associated with radiographic SIJ progression in patients with complete covariate data (N=302, baseline characteristics also shown in table 1). With progression defined as a change of at least 1 grade in at least one SIJ over 2 years and ignoring a change from 0 to 1, a total of 22 progression events were observed during overall 483 X-ray intervals in this

Table 2 Rate of changes in the binary sacroiliac joint outcome measure

Outcome	X-ray intervals of 2 years ± 6 months 894 intervals in 515 patients	
	Intervals with potential progression N=703	Intervals with potential regression N=867
Main analysis: 2 readers*		
Progression	24 (3.4%)	
Regression		1 (0.12%)
Sensitivity analysis: integrating a third scoring†		
Progression	105 (14.9%)	
Regression		21 (2.4%)

*Change considered on agreement of both primary readers.
†Change considered on agreement in 2/3 readings. Progression defined as worsening of at least one grade in at least one SIJ and ignoring a change from 0 to 1 over 2 years; regression defined as improvement of at least one grade in at least one SIJ and a baseline value of at least two in the improved joint.

population. Progression from nr-axSpA to r-axSpA was observed in 16 intervals by reader 1 and in 11 intervals by reader 2 (only one interval with agreement). In patients with multiple 2-year intervals, 36/181 intervals were not consecutive. Prior TNFi use up to the X-ray interval was observed at start of 240/483 X-ray intervals (49.7%). The length of treatment was ≥4 years for 112 of these intervals. No prior TNFi treatment or already discontinued TNF treatment was used as a reference in our model and observed at start of 243 X-ray intervals (203 intervals in TNFi-naïve patients and 40 intervals in patients having discontinued TNFi, respectively). Use of TNFi up to the radiographic interval was associated with less progression in this model (OR 0.21, 95% CI 0.07 to 0.65; table 3). Baseline sacroiliac damage, male sex and disease duration were independently associated with more severe radiographic progression in this model (table 3). Sex differences in SIJ progression are also exemplified by the fact that only 4/22 progression events occurred in women, although 38.4% of radiographic intervals originated from women. None of the women demonstrating progression was treated with TNFi prior to the respective radiographic interval. Substituting BASDAI and CRP for ASDAS did not substantially affect the estimated effect of TNFi on progression (table 4). There was no significant interaction between treatment with TNFi and treatment with NSAIDs, suggesting no additional impact of concomitant treatment with NSAIDs (online supplemental table S3). We found a trend for an additive inhibitory effect for each additional year of TNFi treatment (OR 0.84, 95% CI 0.66 to 1.07, online supplemental table S4).

The impact of TNFi prior to the radiographic interval on progression was only slightly affected by adjusting for ASDAS before treatment start, performed to address the issue of confounding by indication (OR 0.15, 95% CI 0.04 to 0.56, table 5). The retardation of SIJ radiographic progression associated with the use of TNFi prior to the radiographic interval was confirmed when progression was defined as a change in the SSS over 2 years (−0.118 units, 95% CI −0.203 to −0.033; table 6). Current smoking was associated with a significantly higher change in SSS in this model (table 6).

Table 3 Multivariable analysis for identification of factors associated with radiographic SIJ progression defined as a change of at least one grade in at least one SIJ and ignoring a change from 0 to 1 over 2 years

Variable	OR	95% CI	P value
Prior TNFi use up to the start of X-ray interval yes/no	**0.21**	**0.07 to 0.65**	**0.006**
Baseline sacroiliac damage (0–7) at start of each X-ray interval	**1.35**	**1.02 to 1.77**	**0.04**
Female sex	**0.26**	**0.07 to 0.94**	**0.04**
Symptom duration	**1.06**	**1.01 to 1.10**	**0.01**
Current smoking	2.47	0.75 to 8.11	0.14
HLA-B27 negative	0.88	0.18 to 4.35	0.87
NSAID use at start of each X-ray interval	0.86	0.25 to 2.98	0.81
ASDAS at start of each X-ray interval	1.06	0.62 to 1.81	0.82

Analysis in 302 patients and 483 X-ray intervals (22 events).
ASDAS, Ankylosing Spondylitis Disease Activity Score; HLA-B27, human leucocyte antigen B27; NSAID, non-steroidal anti-inflammatory drug; SIJ, sacroiliac joint; TNFi, tumour necrosis factor inhibitor.

Table 4 Sensitivity analysis for identification of factors associated with radiographic SIJ progression with alternative disease activity parameters

Variable	OR	95% CI	P value
Prior TNFi use up to the start of X-ray interval yes/no	**0.22**	**0.08 to 0.60**	**0.003**
Baseline sacroiliac damage (0–7) at start of each X-ray interval	**1.32**	**1.00 to 1.75**	**0.047**
Female sex	0.27	0.07 to 1.04	0.06
Symptom duration	**1.06**	**1.01 to 1.10**	**0.01**
Current smoking	2.46	0.75 to 8.11	0.14
HLA-B27 negative	0.77	0.16 to 3.83	0.75
NSAID use at start of each X-ray interval	0.90	0.26 to 3.10	0.86
BASDAI at start of each X-ray interval	1.02	0.81 to 1.29	0.88
CRP at start of each X-ray interval	1.01	0.98 to 1.04	0.55

Analysis in 302 patients and 483 X-ray intervals (22 events).
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; HLA-B27, human leucocyte antigen B27; NSAID, non-steroidal anti-inflammatory drug; SIJ, sacroiliac joint; TNFi, tumour necrosis factor inhibitor.

We next investigated whether the use of TNFi during a 2-year radiographic interval had an impact on radiographic progression using the binary primary outcome. Out of a total 483 X-ray intervals, there was no TNFi use at all during 144 intervals, TNFi use for at least 1 year in 314 intervals, and TNFi use for <1 year in 25 intervals. Use of TNFi during the radiographic interval was associated with lower odds of progression, but the difference reached statistical significance only if biological treatment was used for more than 1 year (OR 0.21, 95% CI 0.08 to 0.55 vs OR 0.38, 95% CI 0.04 to 3.39 for TNFi use <1 year; table 7). Retardation of SIJ radiographic progression was also found with the use of TNFi during the X-ray interval when progression was defined as a change in the SSS over 2 years (online supplemental table S5).

Sensitivity analyses after integration of a third reading of radiographs

Finally, we analysed the primary outcome after integrating a third reading of the radiographs and considering a change in the binary SIJ outcome measure if it was observed in 2/3 readings. Measurement error of SIJ scoring was more clearly exemplified in this second approach by a higher progression as well as regression rate (table 2). Use of TNFi before the radiographic interval and for at least 1 year during the radiographic interval was associated with significant lower odds for radiographic progression (OR 0.50, 95% 0.28 to 0.89 and OR 0.46, 95% CI 0.27 to 0.78, respectively, in these adjusted longitudinal analyses, table 8).

DISCUSSION

Our findings support the concept of TNFi being able to retard radiographic progression at the level of the SIJ.[11] We took advantage of the same large national observational cohort of patients with axSpA and a similar methodology that enabled us to demonstrate deceleration of spinal radiographic progression in r-axSpA previously,[24] while spinal progression in nr-axSpA was too limited to enable any inhibition to be identified.[9] From the different definitions of progression that have been

Table 5 Impact of *pretreatment* Ankylosing Spondylitis Disease Activity Score (ASDAS) on spinal radiographic progression introduced to address the issue of confounding by indication

Variable	OR	95% CI	P value
Prior TNFi up to the start of X-ray interval yes/no	**0.15**	**0.04 to 0.56**	**0.01**
Baseline sacroiliac damage (0–7) at start of each X-ray interval	1.26	0.92 to 1.72	0.16
Female sex	0.31	0.06 to 1.52	0.15
Symptom duration	1.05	1.00 to 1.11	0.05
Current smoking	2.29	0.56 to 9.40	0.25
HLA-B27 negative	1.07	0.17 to 6.66	0.95
NSAID use at start of each X-ray interval	0.71	0.18 to 2.83	0.63
ASDAS at start of TNFi and ASDAS at inclusion for non-treated patients	1.06	0.62 to 1.81	0.82

Analysis in 226 patients and 352 X-ray intervals (16 events).
ASDAS, Ankylosing Spondylitis Disease Activity Score; HLA-B27, human leucocyte antigen B27; NSAID, non-steroidal anti-inflammatory drug; SIJ, sacroiliac joint; TNFi, tumour necrosis factor inhibitor.

Table 6 Multivariable analysis for identification of factors associated with radiographic SIJ progression defined as a change in the sacroiliitis sum score over 2 years

Variable	Estimate	95% CI
Prior TNFi use up to the start of X-ray interval yes/no	**−0.118**	**−0.203 to −0.033**
Baseline sacroiliac damage (0–7) at start of each X-ray interval	−0.017	−0.041 to 0.207
Female sex	−0.081	−0.170 to 0.007
Symptom duration	0.001	−0.004 to 0.005
Current smoking	**0.087**	**0.001 to 0.173**
HLA-B27 negative	0.084	−0.038 to 0.207
NSAID use at start of each X-ray interval	−0.018	−0.112 to 0.077
ASDAS at start of each X-ray interval	0.011	−0.034 to 0.056

Analysis in 302 patients and 483 X-ray intervals (22 events).
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; HLA-B27, human leucocyte antigen B27; NSAID, non-steroidal anti-inflammatory drug; SIJ, sacroiliac joint; TNFi, tumour necrosis factor inhibitor.

described for the mNY grading system,[6–8] we have chosen the one that proved to be the most sensitive to change[8 21]: worsening of ≥1 grade in ≥1 SIJ and ignoring a change from 0 to 1 over 2 years. Moreover, progression between nr-axSpA and r-axSpA during a 2-year interval is low,[7] and the existing cut-off differentiating them proved of limited benefit to predict important outcomes in a recent analysis of our cohort.[22]

Recognition of structural damage according to the mNYc is subject to considerable inter-reader and intra-reader variation.[25] In line with this observation, not only progression, but also regression in the SIJ score has been detected, most likely reflecting measurement error.[7 8 26] This background 'noise' might be due or amplified by several factors: the quality of the films, the complex anatomy of the SIJs, bowel content overlapping/obscuring the view on SIJs, and the fact that the definition of the individual grades of the score is partly open to interpretation. To be able to estimate 'true' progression, worsening as well as improvement in the score has to be accounted for. In the context of the analysis of potential inhibition of progression, however, concentration on undoubtful images might be of some interest. We have therefore chosen a conservative approach with only two scorers blinded to the chronology of the images and defined progression if both readers agreed on the outcome. A different scoring approach with two readers knowing the sequence of images was chosen by Torgutalp *et al* in their analysis of the German Spondyloarthritis inception cohort (GESPIC) .[11] The fact that retardation of progression by TNFi was found independently of the scoring method adds to the validity of the results. Integration of a third reading in our analysis—with progression defined if the primary outcome was observed in 2/3 readings—allowed for more adequate information on the extent of the measurement error. While in both our analyses, use of TNFi was associated with a lower radiographic SIJ progression, the size of the estimate decreased with an increase in background noise.

Regardless of the approach used (two or three readings), there was at least a 50% decrease in the odds of progressing by at least one grade in one SIJ over 2 years, after excluding a change from grade 0 to grade 1, in patients treated with TNFi before a 2-year radiographic interval. Male sex was associated with a significantly higher rate of progression. While women contributed to almost 40% of radiographic intervals, only 4/22 progression events were found in female patients and none of them was treated with TNFi prior to the respective

Table 7 Impact of TNFi use within a 2-year radiographic interval on sacroiliac joint radiographic progression defined as a change of at least one grade in at least one SIJ and ignoring a change from 0 to 1

Variable	OR	95% CI	P value
TNFi use during X-ray interval ≥1 year (ref: no TNFi use during interval)	**0.21**	**0.08 to 0.55**	**0.001**
TNFi use during X-ray interval <1 year (ref: no TNFi use during interval)	0.38	0.04 to 3.39	0.39
Baseline sacroiliac damage at start of each X-ray interval (0–7)	**1.33**	**1.00 to 1.77**	**0.047**
Female sex	**0.27**	**0.07 to 1.00**	**0.05**
Symptom duration	**1.05**	**1.01 to 1.10**	**0.02**
Current smoking	2.21	0.71 to 6.89	0.17
HLA-B27 negative	0.71	0.14 to 3.81	0.70
NSAID use at start of each X-ray interval	0.93	0.26 to 3.37	0.91
ASDAS at start of each X-ray interval	1.30	0.75 to 2.27	0.35

302 patients and 483 intervals (22 events).
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; HLA-B27, human leucocyte antigen B27; NSAID, non-steroidal anti-inflammatory drug; SIJ, sacroiliac joint; TNFi, tumour necrosis factor inhibitor.

Table 8 Sensitivity analysis: integrating a third reading of radiographs for the multivariable analysis for identification of factors associated with radiographic SIJ progression defined as a change of at least one grade in at least one SIJ and ignoring a change from 0 to 1

	A.TNFi use before the 2-year radiographic interval			B.TNFi use during the 2-year radiographic interval		
Variable	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Prior TNFi use up to the start of X-ray interval yes/no	**0.50**	**0.28 to 0.89**	**0.02**			
TNFi use during X-ray interval≥1 year				**0.46**	**0.27 to 0.78**	**<0.01**
TNFi use during X-ray interval<1 year				0.57	0.18 to 1.84	0.35
Baseline sacroiliac damage at start of each X-ray interval (0–7)	1.12	0.97 to 1.29	0.12	1.11	0.97 to 1.28	0.13
Female sex	0.74	0.44 to 1.26	0.27	0.73	0.43 to 1.26	0.26
Symptom duration	1.00	0.97 to 1.03	0.99	1.00	0.97 to 1.03	0.93
Current smoking	1.29	0.76 to 2.18	0.35	1.23	0.73 to 2.08	0.43
HLA-B27 negative	**1.99**	**1.04 to 3.80**	**0.04**	**1.91**	**1.00 to 3.66**	**0.05**
NSAID use at start of each X-ray interval	0.72	0.40 to 1.29	0.27	0.71	0.40 to 1.28	0.26
ASDAS at start of each X-ray interval	0.85	0.64 to 1.14	0.28	0.95	0.72 to 1.25	0.69

Three hundred one patients with 477 intervals (87 events).
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; HLA-B27, human leucocyte antigen B27; NSAID, non-steroidal anti-inflammatory drug; SIJ, sacroiliac joint; TNFi, tumour necrosis factor inhibitor.

radiographic interval. As a consequence, the study was underpowered to report a separate effect of treatment with TNFi on progression in women. There is a fundamental need for larger and longer studies to assess whether our findings can also be confirmed in a female population.

Interestingly, use of TNFi for at least 1 year during the 2-year X-ray interval was associated with a comparably lower SIJ radiographic progression. This is in contrast to the analysis performed in the GESPIC cohort, in which only treatment in the previous radiographic interval, but not in the current interval was associated with deceleration of progression.[11] The outcome of progression chosen here, however, could not be analysed thoroughly in GESPIC, as there was no progression according to this definition in patients who received TNFi for at least 12 months neither in the previous nor the current radiographic interval.[11] Moreover, no TNFi use during the whole radiographic interval was used as a reference for the use of ≥1 year and <1 year in our analysis, whereas TNFi use during less than 1 year was combined with no TNFi use to provide reference for TNFi use≥1 year in the German cohort. Our findings corroborate results of a study comparing progression in patients treated with etanercept with a contemporary control group in the observational French DESIR cohort, after adjustment for potential confounders.[27]

Slowing of progression was shown here not only for the chosen binary outcome, but also for the continuous SIJ score in the mNY grading system. We did not choose the latter as a primary outcome, as the grading steps in this semiquantitative system cannot be regarded as being equidistant. The difference in progression of −0.12 units of the SSS between TNFi-treated and untreated patients is, therefore, more difficult to interpret. A very comparable estimate of −0.09 units has been demonstrated in the German cohort for patients treated for at least 12 months with TNFi in the previous interval in comparison to untreated patients.[11] To put this into perspective, our findings can also be compared with a recent study of SIJ radiographic progression in patients treated with etanercept over 6 years: a mean change of+0.20 units was detected during the first 2 years, followed by a change of −0.22 units between year 2 and 4 and −0.09 units between year 4 and 6.[28]

It has been argued that SIJ radiographic progression is of limited functional relevance,[12] as an increase in one radiographic sacroiliitis grade in one joint was only associated with a functional deterioration of 0.1 BASFI points.[29] The significance of spinal structural damage on impairments in physical function are, in contrast, beyond controversy.[30] Formation of spinal syndesmophytes in axSpA can occur in the absence of definite sacroiliac changes in a limited proportion of patients and could affect function and mobility.[31] We could not assess this issue here, as spinal radiographs were not available in all patients. While 8 out of 88 patients with nr-axSpA had at least one syndesmophyte in our previous analysis of spinal radiographic progression in our cohort,[9] only one patient had a modified Stoke Ankylosing Spondylitis Spinal Score (range 0–72) >10. Axial inflammation is expected, therefore, to have a much higher impact on function and mobility in nr-axSpA than the very limited structural damage documented. As more severe SIJ postinflammatory changes are associated with much higher baseline spinal osteoproliferative changes as well as with spinal radiographic progression,[9] deceleration of SIJ structural damage might imply in the context of a

continued treatment with TNFi a further retardation of spinal progression and the expected later impairments in function, mobility and health-related quality of life.[30]

The lack of MRI data paralleling X-ray data represents the major limitation of our analysis, but is inherent to the observational data of this cohort, gathered in>50% of patients from private rheumatology practices.[32] We do not have information on the proportion and the characteristics of patients not participating in SCQM. Moreover, the need for at least two radiographic assessments to analyse progression biased the study population towards a slightly less severe disease phenotype. We can only speculate about the reasons of these differences. The presence of sequential radiographs might indicate a more compliant patient population with regular consultations with the rheumatologist, more frequent approval of non-pharmacological and pharmacological treatment recommendations and, therefore, lower disease activity. At least with regard to the population with complete covariate data, baseline characteristics were comparable to the whole population in which SIJ radiographic progression could be assessed.

In conclusion, our data suggest that treatment with TNFi in axSpA has a significant inhibitory effect on SIJ radiographic progression if treatment is continued for at least 1 year.

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