Delayed treatment with a tumor necrosis factor alpha blocker associated with worse outcomes in patients with spondyloarthritis: data from the Czech National Registry ATTRA

Tomas Milota(iD)**, Jana Hurnakova, Karel Pavelka, Zlatuse Kristkova, Lucie Nekvindova and Rudolf Horvath**

Abstract

Introduction: The administration of biologic disease-modifying antirheumatic drugs, including tumor necrosis factor (TNF)-α inhibitors, is observed to interfere with the disease activity and progression. In this study, we aimed to assess the effectiveness and response predictors of adalimumab (ADA), a TNF-α blocker, in patients with axial spondyloarthritis (AxSpA).

Methods: This study was a historical prospective, registry-based observational study on patients with AxSpA treated with first-line ADA after conventional drug failure. For evaluation and comparison, patients were divided into three groups according to the number of years from AxSpA diagnosis to initiation of ADA treatment: (A) <5 years, (B) 5–10 years, and (C) >10 years. The assessment instruments ankylosing spondylitis disease activity score (ASDAS), Bath ankylosing spondylitis activity index (BASDAI), Bath ankylosing spondylitis functional index (BASFI), health assessment questionnaire (HAQ), Short Form 36 questionnaire (SF-36), and EuroQoL 5 dimension questionnaire (EQ-5D) were regularly administered for up to 24 months of follow-up.

Results: This study included 1043 patients with AxSpA (9.2% with non-radiographic AxSpA, 68.9% men). By month 6, a significantly higher proportion of patients with ASDAS remission (<1.3) was achieved upon earlier intervention in group A (30.1%) and B (32.9%) than in the late intervention group C (22.6%) ($p \leqslant 0.05$). At month 6, lower age and better BASFI at treatment initiation were identified as the strongest predictors of ASDAS remission in both univariable [odds ratio (OR): 0.956, $p \leqslant 0.001$; OR: 0.834, $p \leqslant 0.001$, respectively] and multivariable analyses (OR: 0.963, $p \leqslant 0.001$; OR: 0.859, $p \leqslant 0.001$, respectively). Earlier intervention also led to improvement in most patient-reported outcomes (PROs) based on HAQ, SF-36, and EQ-5D.

Conclusion: Results from the ATTRA registry concur with previous clinical trials that supported efficacy of TNF-α blockers and showed better treatment outcomes with early interventions, including reduction of disease activity and improvement in PROs. We identified age and BASFI as the main factors influencing treatment effectiveness.

Keywords: adalimumab, ankylosing spondylitis, axial spondyloarthritis, disease activity, patient-reported outcomes

Correspondence to:
Rudolf Horváth
Department of Pediatric and Adult Rheumatology, Motol University Hospital, V Úvalu 84, Prague 150 06, Czech Republic.
rudolf.horvath@fnmotol.cz

Tomas Milota
Department of Pediatric and Adult Rheumatology, Motol University Hospital, Prague, Czech Republic

Department of Immunology, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic

Jana Hurnakova
Department of Pediatric and Adult Rheumatology, Motol University Hospital, Prague, Czech Republic

Karel Pavelka
Institute of Rheumatology and Department of Rheumatology, First Faculty of Medicine, Charles University, Prague, Czech Republic

Zlatuse Kristkova
Institute of Biostatistics and Analyses, Ltd [a spinoff company of Masaryk University], Brno, Czech Republic

Lucie Nekvindova
Institute of Rheumatology and Department of Rheumatology, First Faculty of Medicine, Charles University, Prague, Czech Republic

Institute of Biostatistics and Analyses, Ltd [a spinoff company of Masaryk University], Brno, Czech Republic

Introduction

Randomized clinical trials (RCTs)-based evidence provides compelling data on the efficacy and safety of the tumor necrosis factor-α (TNF-α) blockers including adalimumab (ADA) in patients with spondyloarthritis.[1–8] Disease activity reduction,
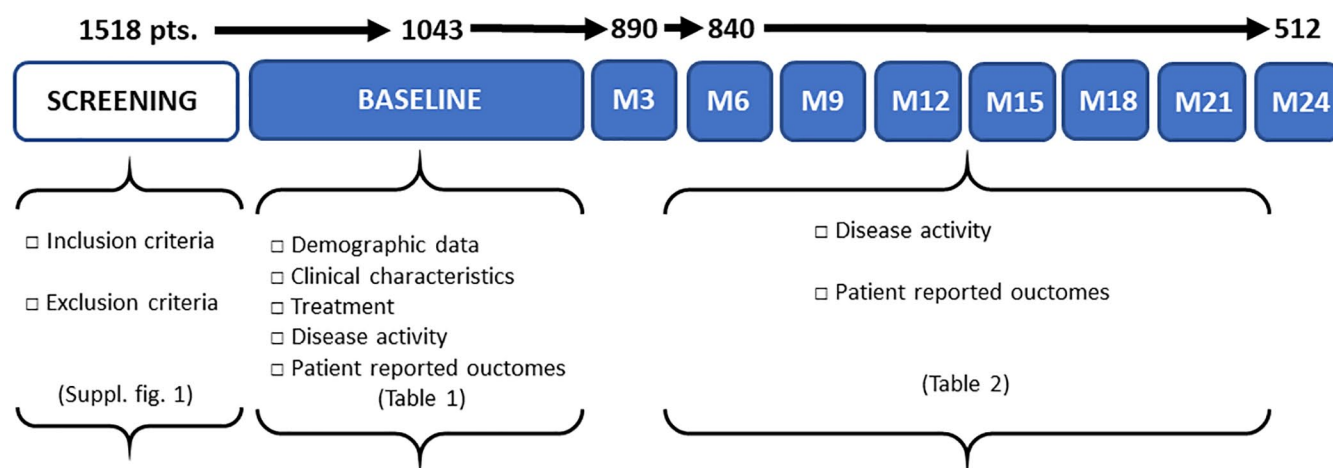
Figure 1. Study design: screening period (assessment of inclusion and exclusion criteria, summarized in 'Supplemental Figure 1'), baseline (collection of patient and clinical characteristics, summarized in Table 1), study time points M (Month) 3, M6 and End of study at M24 (assessment of disease activity and patient-reported outcomes, summarized in Table 2), number of patients (pts.) at different time points displayed.

symptom relief, and corresponding improvements in functional status and patient-reported outcomes (PROs), along with a satisfactory safety profile, have led to the widespread use of TNF-α blockers in patients refractory or intolerance to conventional therapies.[9–12] In addition, the administration of biologic disease-modifying antirheumatic drugs (bDMARDs), including TNF-α inhibitors, can interfere with the structural progression of the disease, thus preserving the functional status and mobility of the patients in the long run.[13–15] In line with this, the concept of having a 'window of opportunity' in axial spondyloarthritis (AxSpA) has been discussed.[16–18] Despite improvements in the field of AxSpA, many unanswered questions remain, including when to start targeted therapies, such as cytokine inhibition.[19–21] RCTs of TNF-α blockers in early AxSpA have yielded encouraging results, with greater treatment responses than in disease of longer duration, suggesting a favorable impact on both disease activity and radiographic progression.[22–26] However, it is debatable whether the RCT evidence allows comparison and generalization to common practice, notably when therapeutic responses in the real world appear to be significantly less. This might be caused by selection bias originating with the enrollment of patients into RCTs, resulting in a sample biased toward better education, higher socioeconomic status, and better mental or overall health.[27] On the contrary, clinical registries handle relatively unselected patient groups, thus preserving valuable information on the effectiveness and safety of the studied treatments in real-world settings.

In our historical prospective analysis of the Czech National Registry ATTRA, we conducted a detailed analysis and comparison of three subgroups of patients with AxSpA treated with first-line ADA, after the failure of conventional drug therapy. The subgroups were defined by the length of the interval between AxSpA diagnosis and initiation of ADA therapy. We hypothesized that earlier interventions would lead to better treatment outcomes reflected in reduced disease activity and improved PROs. We also aimed to identify the baseline factors strongly associated with treatment success using univariate and multivariate analyses.

Methods

Study population
The ATTRA registry deals with collected anonymized clinical data, and all subjects enrolled in the study provided written consent for participation. The ATTRA registry historical prospective observational study was approved by the Czech Multicenter Research Ethics Committee (no. 201611S300). The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. The study design is summarized in Figure 1.

From the 1518 identified adult patients meeting the modified New York criteria for ankylosing spondylitis and the Assessment of Spondyloarthritis International Society criteria for AxSpA[28] and

treated with ADA, 1043 subjects were selected for further analysis. The remaining patients (475) were excluded based on exclusion criteria: (1) patients treated with ADA prior to entry into the registry, (2) juvenile form (≤16 years of age) of AxSpA, (3) patients treated with different biologics prior to ADA, and (4) unknown date of diagnosis (Supplemental Figure 1). The enrollment period was from 1 January 2006 to 1 January 2018 (Supplemental Figure 2). Both radiographic (*N* = 947; 90.8%) and non-radiographic (*N* = 96; 9.2%) patients were included. All analyzed participants were treated with ADA as the first-line bDMARD after failure or intolerance to conventional treatment before. Conventional treatment was defined as the use of two different nonsteroidal anti-inflammatory drugs in maximal therapeutic doses, each for ≥4 weeks. Comparison and analysis were performed across three study groups defined by the length of the interval between the AxSpA diagnosis and the initiation of TNF-α inhibitor treatment. These three subgroups were characterized based on the onset of intervention, as follows: A, early (<5 years; *N* = 511; 49%); B, mid (5–10 years; *N* = 240; 23%); and C, late (>10 years; *N* = 292; 28%) intervention.

Treatment response assessment

Treatment effectiveness was evaluated using the ankylosing spondylitis disease activity score (ASDAS)[29] and the Bath ankylosing spondylitis activity index (BASDAI).[30] Disease remission was defined as an ASDAS score <1.3. PROs were assessed using the Bath ankylosing spondylitis functional index (BASFI),[31] the health assessment questionnaire (HAQ), the SF-36 (short-form 36 health survey), and the EuroQoL-5 dimension questionnaire (EQ-5D).[32] In the analysis identifying the strongest predictors associated with treatment success using univariate and multivariate models, ASDAS remission (score <1.3) and BASDAI 50 (a BASDAI score improvement of 50%) at month 6 were defined as primary targets. The laboratory inflammation markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were assessed. All evaluations were performed at 3-month intervals for up to 24 months of follow-up.

Statistical analysis

A descriptive summary of patient characteristics was generated for all three subgroups. The available case analysis without imputation was performed. The median with 5th and 95th percentiles and the mean with standard deviation (SD) were calculated for continuous parameters. Absolute and relative frequencies (i.e. percentages) were used to describe categorical variables. We performed non-parametric Kruskal-Wallis testing for continuous variables and Pearson chi-square testing for categorical variables to test for significant differences among the three subgroups. We employed post hoc analysis to discover which subgroups differed in the tested parameters. Bonferroni corrections were used to control for multiple testing. Drug retention was calculated using the Kaplan–Meier method. The estimated probabilities of drug retention were compared using the log-rank test. Two survival curves were compared at a fixed point using the test described by Klein *et al.*[33] For all tests, a *p*-value ≤ 0.05 was considered significant. Predictive factors for both remission achievement (ASDAS < 1.3) and major clinical response BASDAI 50 were evaluated using univariable and multivariable logistic regression models. Statistically significant parameters from univariable models were put into the multivariable model with respect to correlation after clinical consideration. Regression results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The analysis was performed using IBM Statistics 25.0 and R (version 3.5.3).

Results

Patient baseline characteristics

The baseline characteristics are described in Table 1. As expected, majority of patients in Groups A, B, and C were male (66.9%, 69.2%, and 72.3%, respectively) with the radiographic form of AxSpA and were positive for the class I major histocompatibility allele HLA-B27 (87.4%, 89.4%, and 95.5%, respectively). Age and disease duration were significantly different across groups (A: 35.1 years ± 9.9 SD, B: 32.5 years ± 10.1 SD, C: 28.4 years ± 9.1 SD), wherein group A has the highest mean age and shortest disease duration (A: 1.8 years ± 1.4 SD; B: 7.3 years ± 1.4 SD; C: 18 years ± 7.6 SD). Similarly, the lowest age of ADA initiation was recorded for group A (37.0 years ± 9.9 SD), when compared with groups B (39.8 years ± 9.9 SD) and C (46.4 years ± 10.4 SD). Interestingly, the patient groups did not differ at baseline in disease activity measured using the BASDAI (A: 6.3 ± 1.6 SD; B: 6.2 ± 1.8 SD; C: 6.6 ± 1.6 SD), ASDAS (A: 4.0 ± 0.8 SD; B: 4.0 ± 0.8 SD; C: 4.2 ± 0.8 SD), or ESR (A: 31.6 mm/h ± 20.5 SD; B: 33.0 ± 19.1

Table 1. Baseline patient characteristics.

Parameter	Group A (*N* = 511)	Group B (*N* = 240)	Group C (*N* = 292)
Sex (male, %)	66.9	69.2	72.3
Age at diagnosis (years, mean ± SD)	35.1 ± 9.9	32.5 ± 10.1	28.4 ± 9.1
Age at BT initiation (years, mean ± SD)	37.0 ± 9.9	39.8 ± 9.9	46.4 ± 10.4
Disease duration (years, mean ± SD)	1.8 ± 1.4	7.3 ± 1.4	18.0 ± 7.6
HLA-B27 positivity (%)	87.4	89.4	95.5
Solely axial involvement (%)	46.4	37.4	34.5
Peripheral involvement (%)	53.6	62.6	65.5
Previous use of csDMARDs (%)	61.5	69.3	76.6
Previous use of GCs (%)	37.5	37.2	47.6
csDMARDs at baseline (%)	38.4	39.2	38.4
GCs at baseline (%)	17.8	15.4	15.4
CRP (mg/L, mean ± SD)	23.7 ± 22.4	26.1 ± 20.4	26.8 ± 22.8
ESR (mm/h, mean ± SD)	31.6 ± 20.5	33.0 ± 19.1	35.7 ± 22.3
ASDAS (mean ± SD)	4.0 ± 0.8	4.0 ± 0.8	4.2 ± 0.8
BASDAI (mean ± SD)	6.3 ± 1.6	6.2 ± 1.8	6.6 ± 1.6
BASFI (mean ± SD)	5.3 ± 2.2	5.2 ± 2.2	5.9 ± 2.2
HAQ (mean ± SD)	1.1 ± 0.5	1.1 ± 0.5	1.3 ± 0.5
EQ-5D (mean ± SD)	0.3 ± 0.3	0.3 ± 0.3	0.3 ± 0.3

ASDAS, ankylosing spondylitis disease activity score; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing functional index; BT, biological treatment; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; EQ-5D, EuroQoL 5 dimension questionnaire; ESR, erythrocyte sedimentation ratio; GCs, glucocorticosteroids; HAQ, health assessment questionnaire.
Groups are defined by years from diagnosis to treatment initiation: Group A, <5 years; Group B, 5–10 years; Group C, >10 years.

SD; C: 35.7 ± 22.3 SD). Only slight differences in CRP levels were found (A: 23.7 mg/L ± 22.4 SD; B: 26.1 ± 20.4 SD; C: 26.8 ± 22.8 SD). Meanwhile, group A had a higher proportion of patients with a solely axial manifestation (46.4% *versus* 37.4% and 34.5%, respectively) and a corresponding lower use of conventional synthetic disease-modifying antirheumatic drugs and glucocorticoids in the past compared to group C. Patients in group C had the worst functional status as measured with BASFI, which was supported by the HAQ results and some of the reported SF-36 domains (i.e. physical functioning, bodily pain, general health perceptions, social role functioning, and mental health). The

baseline value from the EQ-5D showed no differences across groups.

Effectiveness
Table 2 highlights the effectiveness of treatments. The baseline median BASDAI and ASDAS values for all three subgroups reflected high disease activity in most of the patients (approximately 93% of the subjects had baseline BASDAI >4, and approximately 99% had an ASDAS above 2.1). Following ADA treatment initiation, the mean BASDAI values dropped across all three groups within the first 3 months; however, significant differences between the groups A (2.8 ± 1.9 SD) and

B $(2.7 \pm 2.0$ SD) compared with group C $(3.3 \pm 1.9$ SD) were observed. The mean values then subsequently decreased, while intergroup differences remained unchanged after 24 months, with group C having the worst results. Similar trends and significances were observed in ASDAS (A: 1.9 ± 0.9 SD; B: 2.0 ± 0.9 SD; C: 2.1 ± 0.9 SD), with patients in group C having the worst results after the 2-year treatment. In contrast, the drug retention rate was not affected by the time of treatment initiation (Figure 2).

The proportion of patients persisting on treatment and who achieved inactive disease (ASDAS <1.3) measured at month 6 was significantly higher $(p \leqslant 0.05)$ in groups A and B compared with group C. The differences were observed at months 12 and 18 as well (Figure 3). Similarly, achieving BASDAI 50 occurred in a significantly higher number of patients in groups A and B than in group C $(p \leqslant 0.05)$ at month 6. Moreover, the differences were observed at months 3 and 12 (Figure 4).

PROs
The outcomes of all PROs are summarized in Table 2. Baseline BASFI after treatment initiation improved in all analyzed patients; however, group C had the worst results and showed significant differences with groups A and B. This was maintained during 2 years of follow-up.

HAQ values also significantly improved with ADA treatment. However, the differences between group C and the others remained unchanged and were consistent during the 2-year follow-up period.

After 3 months of ADA treatment, groups A and B responded the best in the EQ-5D, and group C had the worst response, which was statistically significant. The long-term trend followed the trend of the HAQ.

Following 1 year of ADA treatment, improvements across all reported domains were observed in the PRO SF-36, with statistical significance between groups A and B compared with group C in physical functioning and in group A compared with group C in the domains of global health and social functioning.

Baseline predictors of the treatment response
In the next part of the analysis, we aimed to identify baseline predictors for ASDAS remission at

Table 2. Disease activity and patient-reported outcomes.

	Month 3 (N=890)				Month 6 (N=840)				Month 24 (N=512)			
	Group A (N=421)	Group B (N=216)	Group C (N=253)	p-value	Group A (N=393)	Group B (N=199)	Group C (N=248)	p-value	Group A (N=236)	Group B (N=121)	Group C (N=155)	p-value
ASDAS	1.9 ± 0.9	2.0 ± 0.9	2.1 ± 0.9	0.019[a]	1.8 ± 1.0	1.8 ± 1.0	2.0 ± 0.9	0.004[a,b]	1.4 ± 0.8	1.5 ± 0.8	1.9 ± 0.8	<0.001[a,b]
BASDAI	2.8 ± 1.9	2.7 ± 2.0	3.3 ± 1.9	<0.001[a,b]	2.5 ± 1.9	2.4 ± 1.9	2.9 ± 2.0	0.002[a,b]	1.9 ± 1.7	2.0 ± 1.7	2.6 ± 1.8	0.001[a,b]
BASFI	2.7 ± 2.2	2.7 ± 2.3	3.9 ± 2.4	<0.001[a,b]	2.3 ± 2.1	2.3 ± 2.1	3.4 ± 2.4	<0.001[a,b]	1.9 ± 2.0	2.1 ± 2.0	3.1 ± 2.3	<0.001[a,b]
HAQ	0.61 ± 0.52	0.62 ± 0.52	0.88 ± 0.58	<0.001[a,b]	0.54 ± 0.49	0.56 ± 0.51	0.80 ± 0.60	<0.001[a,b]	0.43 ± 0.45	0.46 ± 0.47	0.72 ± 0.52	<0.001[a,b]
EQ-5D	0.70 ± 0.23	0.71 ± 0.25	0.63 ± 0.27	<0.001[a,b]	0.73 ± 0.23	0.74 ± 0.22	0.66 ± 0.26	0.002[a,b]	0.77 ± 0.19	0.77 ± 0.21	0.70 ± 0.20	<0.001[a,b]

ASDAS, ankylosing spondylitis disease activity score; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing functional index; EQ-5D, EuroQoL 5 dimension questionnaire; HAQ, health assessment questionnaire.
Values are presented as mean ± standard deviation. Months 3, 6 and 24 (end of study) = time since treatment initiation.
[a] $p \leqslant 0.05$ between Groups A and C.
[b] $p \leqslant 0.05$ between Groups B and C.
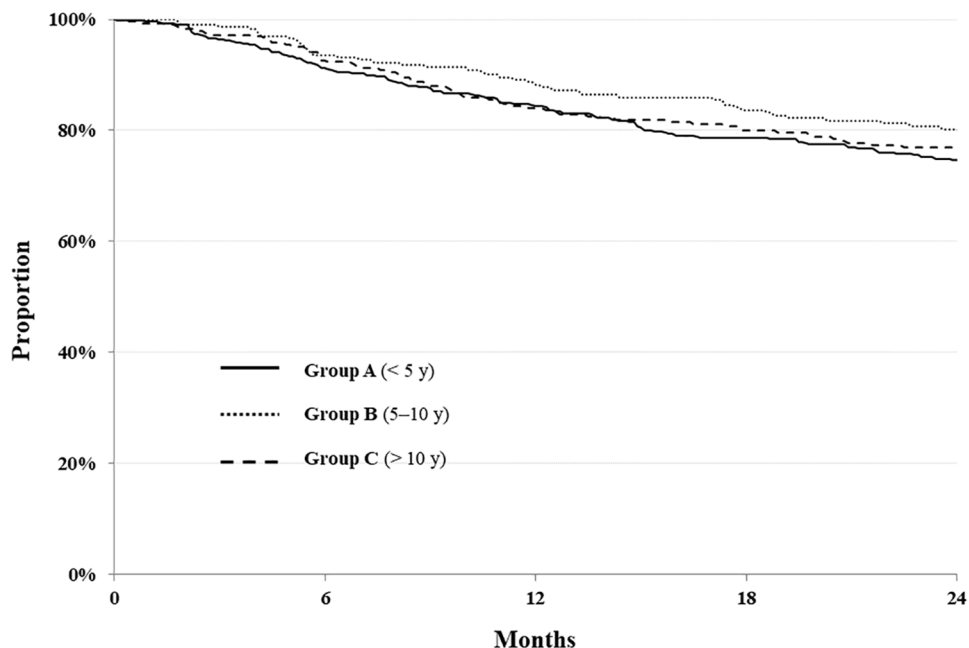[c] $p \leqslant 0.05$ between Groups A and B.

Figure 2. The proportion of patients persisting in adalimumab treatment *versus* treatment follow-up time. Shown are Kaplan–Meier curves. The key indicates the amount of delay from diagnosis of spondyloarthritis to initiation of adalimumab treatment.
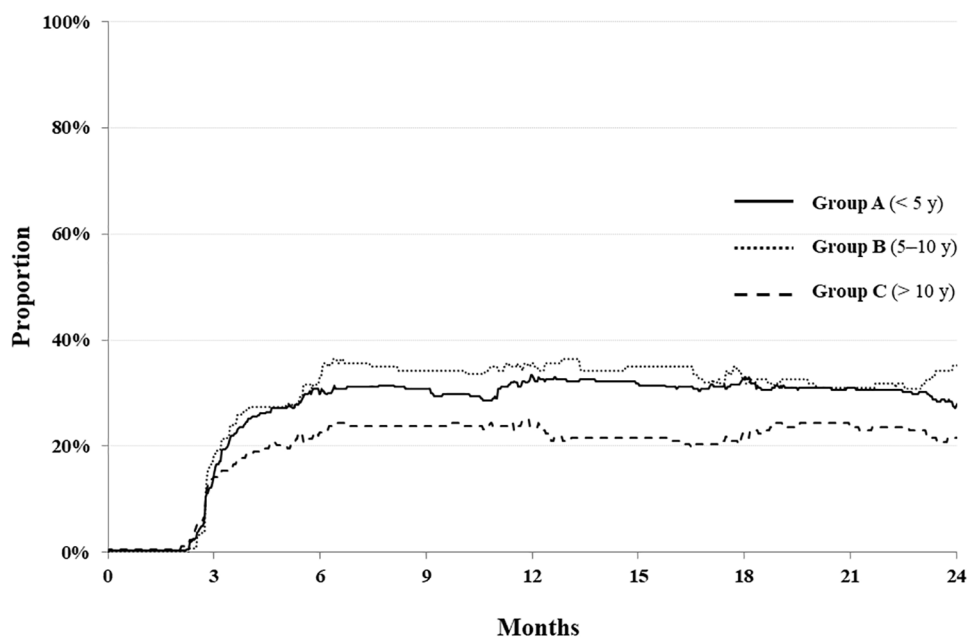

Figure 3. The proportion of patients persisting in treatment who achieve remission (ASDAS < 1.3) *versus* treatment follow-up time. Shown are Kaplan–Meier curves. The key indicates the amount of delay from diagnosis of spondyloarthritis to initiation of adalimumab treatment. ASDAS, ankylosing spondylitis disease activity score.
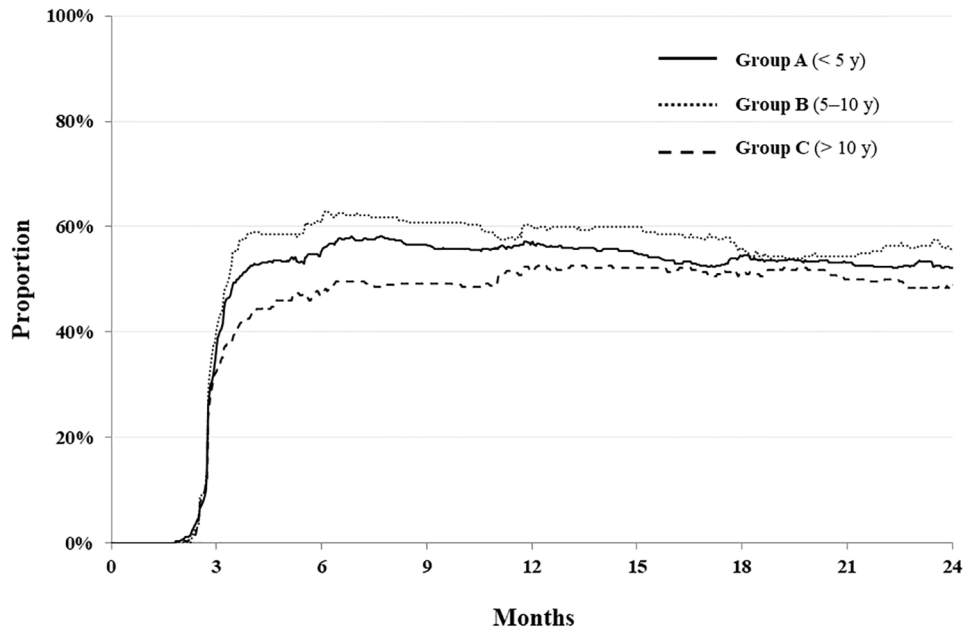
Figure 4. The proportion of patients persisting in treatment who achieve BASDAI 50 *versus* follow-up time. Shown are Kaplan–Meier curves. The key indicates the amount of delay from diagnosis of spondyloarthritis to initiation of adalimumab treatment. BASDAI, Bath ankylosing spondylitis activity index.

month 6. In the univariable models, group C (OR: 0.637, 95% CI: 0.412–0.987), along with other parameters such as female sex (OR: 0.629, 95% CI: 0.431–0.919), higher age at the initiation of ADA treatment (OR: 0.956, 95% CI: 0.939–0.972), and peripheral joint involvement (OR: 0.568, 95% CI: 0.348–0.772), were negatively associated with achieving the endpoint <1.3 (disease remission). Other negative predictors were higher disease activity (i.e. higher BASDAI and ASDAS scores), worse BASFI values, and worse HAQ. Meanwhile, multivariable analysis identified age at the initiation of treatment and worse BASFI values as the strongest negative predictors of achieving ASDAS <1.3 (Table 3).

A slightly different perspective on treatment response predictors is provided by a 50% improvement over baseline values (BASDAI 50), which is used as an alternative measurement tool in AxSpA. Similar to the baseline predictors of ASDAS remission, group C, higher age at ADA treatment initiation, peripheral joint involvement, and worse HAQ values negatively correlated with achieving this endpoint at month 6 in the univariable analysis. In contrast, positive predictors were higher disease activity as assessed by BASDAI and ASDAS and the natural logarithm of CRP. In the multivariable analysis, higher age at the

initiation of ADA treatment, along with worse HAQ, were identified as negative predictors. On the contrary, higher BASDAI and CRP levels predicted a favorable response in achieving the BASDAI 50 endpoint (Table 4).

Discussion

Over the past decades, there has been a general approach of early management in various immune-mediated inflammatory diseases (IMIDs).[34–37] This has been based on the hypothesis that early diagnosis and treatment may better control the underlying inflammatory character of the IMIDs and lead to favorable treatment outcomes, including functional impairment and structural damage. In AxSpA, there is a growing number of RCTs using TNF-α blockers, which show encouraging results in early disease.[22–26] However, these interventions are still lacking in a real-world setting based on the clinical registries data, which support and advocate early bDMARDs treatments in AxSpA. In this study, we aimed to investigate the differences between early-, mid-, and late-stage bDMARD interventions in common practice using prospective analysis of the ATTRA clinical registry. We also aimed to identify baseline predictors of bDMARD treatment success using univariable and multivariable statistical analyses. We included a cohort of more than 1000 patients

Table 3. Treatment response predictors based on remission (ASDAS <1.3).

Endpoint: remission (ASDAS <1.3)		
Predictor	**OR (95% CI)**	***p*-value**
Univariable analysis		
Early treatment intervention (group A)	Ref.	
Mid treatment intervention (group B)	1.18 (0.76–1.78)	0.448
Late treatment intervention (group C)	0.64 (0.41–0.99)	0.043
Age at treatment initiation	0.996 (0.939–0.972)	<0.001
Female sex	0.63 (0.43–0.92)	0.017
Peripheral joint involvement (*versus* axial)	0.57 (0.35–0.77)	<0.001
BASDAI	0.88 (0.79–0.97)	0.015
ASDAS	0.75 (0.6–0.95)	0.015
BASFI	0.83 (0.77–0.90)	<0.001
EQ-5D	2.09 (1.21–3.61)	0.008
SF-36 – role physical	1.02 (1.01–1.02)	<0.001
SF-36 – bodily pain	1.01 (1.00–1.03)	0.023
SF-36 – general health	1.01 (1.00–1.02)	0.049
SF-36 – social functioning	1.01 (1.00–1.02)	0.027
HAQ	0.51 (0.36–0.71)	<0.001
Multivariable analysis		
Age at treatment initiation	0.96 (0.95–0.98)	<0.001
Mid treatment intervention (*versus* Early)	1.28 (0.82–1.98)	0.28
Late treatment intervention (*versus* Early)	0.93 (0.57–1.52)	0.776
Female sex	0.70 (0.47–1.05)	0.083
BASFI	0.86 (0.79–0.93)	<0.001

ASDAS, ankylosing spondylitis disease activity score; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing functional index; CI, confidence interval; EQ-5D, EuroQoL 5 dimension questionnaire; HAQ, health assessment questionnaire; OR, odds ratio; SF-36, Short Form 36 questionnaire.

treated with first-line bDMARD-ADA following conventional drug failure and compared three different patient subgroups stratified by the length of the interval between AxSpA diagnosis and the initiation of treatment with the TNF-α blocker ADA. We decided to use this strategy and prioritize it over stratification by disease length (i.e. the duration from the appearance of the first symptom to AxSpA diagnosis/treatment initiation), since we

believe that treatment with ADA is more accurately reported in the registry, that is, with a significantly lower error rate.[38,39]

In general, we found that early intervention led to significantly better outcomes. This was notable when comparing the effect of ADA on the kinetics of the disease activity as measured with BASDAI or ASDAS, even though the baseline

Table 4. Treatment response predictors based on major clinical response (BASDAI 50).

Endpoint: major clinical response (BASDAI 50)		
Predictor	**OR (95% CI)**	**p-value**
Univariable analysis		
Early treatment intervention (group A)	Ref.	
Mid treatment intervention (group B)	1.09 (0.77–1.54)	0.639
Late treatment intervention (group C)	0.67 (0.49–0.92)	0.013
Age at treatment initiation	0.97 (0.96–0.98)	<0.001
Peripheral arthritis (*versus* axial)	0.61 (0.45–0.84)	0.002
CRP	1.19 (1.01–1.41)	0.04
BASDAI	1.27 (1.16–1.38)	<0.001
ASDAS	1.43 (1.13–1.82)	0.003
SF-36 – physical functioning	1.0 (1.003–1.11)	0.038
SF-36 – general health	1.10 (1.01–1.20)	0.025
HAQ	0.92 (0.87–0.97)	0.001
Multivariable analysis		
Age at treatment initiation	0.97 (0.96–0.99)	<0.001
Mid treatment intervention (*versus* Early)	1.12 (0.77–1.64)	0.556
Late treatment intervention (*versus* Early)	0.83 (0.57–1.21)	0.330
BASDAI	1.46 (1.31–1.62)	<0.001
CRP	1.01 (1.00–1.02)	0.036
HAQ	0.42 (0.30–0.58)	<0.001

ASDAS, ankylosing spondylitis disease activity score; BASDAI, Bath ankylosing spondylitis disease activity index; CI, confidence interval; CRP, C-reactive protein; HAQ, health assessment questionnaire; OR, odds ratio; SF-36, Short Form 36 questionnaire.

disease burden across the studied groups was equal. Both the mid (group B) and late (group C) intervention groups responded less well compared with the early group (group A). Similar patterns were observed when assessing BASFI, HAQ, EQ-5D, and SF-36, although all patients had a significant degree of response. This was constant across all groups during the 2-year follow-up period, which supports early treatment. Our results agree with previous RCT observations where early intervention with ADA[7] and other TNF-α inhibitors[40,41] yielded better outcomes, including a reduction in disease activity and an improvement in functional status.

Moreover, the level of disease activity and functional ability also determine and correlate with the PRO results and quality of life.[11,42–45]

The next part of our analysis focused on defining baseline predictors of the response to 6 months of ADA treatment. Based on our analysis, we showed that earlier interventions with ADA significantly predicted ASDAS remission. Whereas the early and mid groups did not significantly differ, the late intervention group had a significantly lower probability of achieving the endpoint in univariable analysis. Other predictors of poor outcomes were the female sex, older age, higher disease

activity, peripheral joint involvement, worse functional status, and low quality of life. Interestingly, when the significant variables were analyzed in the multivariable statistical model, we found that at month 6, age at treatment initiation and BASFI most affected the achievement of ASDAS <1.3. It was also evident that the age at bDMARD treatment initiation did correlate with the 'group' parameter defined in our analysis, which is clearly seen in the baseline demography data (patients in group C started ADA treatment at a significantly more advanced age than did the first two groups). However, the 'group' parameter lost its statistical impact in the multivariable models, while 'age' gained significance. This is an important point that requires careful interpretation and encourages the initiation of treatment in younger age groups. These findings are also consistent with those of previously published RCTs wherein younger age, male sex, HLA-B27 positivity, higher levels of acute-phase reactants, TNF-α naivety, and lower BASFI were identified as the strongest predictors of good clinical response and disease remission.[46–48] A spectrum of response predictors, such as HLA-B27 positivity (DANBIO registry),[49] obesity (British Society for Rheumatology Biologics Register in Ankylosing Spondylitis),[50] or quality of life (Groningen Leeuwarden Ankylosing Spondylitis cohort),[51] has been demonstrated as factors that significantly influence the efficacy of TNF-α inhibitors in the registry-based studies representing real-world practice. Nevertheless, only very limited data are available on the age and disease duration.

A slightly different perspective can be accessed by using a different endpoint such as BASDAI 50. Again, in the univariable analysis, the early and mid patient groups did not significantly differ; however, the late-stage group had an approximately one-third lesser chance of reaching this endpoint than did the early-stage group A. Other predictors associated with poorer outcomes included more advanced age, peripheral joint involvement, and higher HAQ scores. Interestingly, among the remaining variables, higher baseline disease activity (BASDAI or ASDAS), along with higher CRP, predicted BASDAI 50 improvement. In the multivariable analysis, we observed once more the loss of statistical impact of the 'group' variable on prediction and its transformation into the parameter of age of initiation of bDMARD therapy. The other important defined predictors of achieving this

endpoint were worse HAQ, higher CRP, and higher BASDAI. Similar results have been published by Rudwaleit *et al.*[52] that presented a different point of view on treatment predictors. These findings raise the question of why BASDAI 50 differs from ASDAS remission in identifying predictors of disease activity among baseline measurements. We assume that seemingly more room for improvement exists in patients initially manifesting with a higher disease burden or a higher CRP. Such an improvement certainly could mean a great relief for many of them, and it is presently debated whether improvement or the more stringent achievement of remission would be the optimal outcome for AxSpA in the real world, and whether we need to insist on remission as our only target.[16,53] On the contrary, increased baseline BASDAI scores may be associated with a higher risk of treatment discontinuation.[54] Regardless of the nature of the chosen primary targets, our results support early interventions and a lower age at the initiation of bDMARD therapy, which resulted in the best outcomes. Of course, safety issues and treatment costs must be carefully considered with such strategies. Based on our results, we believe that younger patients will benefit more from bDMARD treatment, as their functional capacity to improve seems to exceed that of the more elderly population. Whether the disease itself behaves and responds differently in younger patients than in elderly patients remains debatable.[55]

Our study has several strengths and limitations. We believe that our included cohort of more than 1000 patients with well-balanced groups can generate quality results. On the contrary, the study was limited to one bDMARD, and it was a retrospective, uncontrolled, and non-randomized design, which might be restrictive. This study provides interesting insights and highlights the success of early interventions with TNF-α blockers in patients with spondyloarthritis.

Author contributions
Tomas Milota: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Resources; Visualization; Writing – original draft; Writing – review & editing.

Jana Hurnakova: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Writing – original draft; Writing – review & editing.

Karel Pavelka: Conceptualization; Data curation; Methodology; Supervision; Writing – review & editing.

Zlatuse Kristkova: Conceptualization; Data curation; Methodology; Project administration; Validation; Visualization; Writing – original draft; Writing – review & editing.

Lucie Nekvindova: Conceptualization; Data curation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing.

Rudolf Horvath: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics statement

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Czech Multicenter Research Ethics Committee (no. 201611S300).

ORCID iD

Tomas Milota https://orcid.org/0000-0003-2105-3462

Data availability statement

Due to confidentiality or sensitivity issues, the deidentified participants' data are available upon reasonable request to ATTRA Clinical Register, Institute of Biostatistics and Analyses, Czech Republic.

Supplemental material

Supplemental material for this article is available online.

References

1. Davis JC Jr, van der Heijde D, Braun J, *et al.* Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003; 48: 3230–3236.

2. Inman RD, Davis JC Jr, van der Heijde D, *et al.* Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum* 2008; 58: 3402–3412.

3. Landewé R, Braun J, Deodhar A, *et al.* Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. *Ann Rheum Dis* 2014; 73: 39–47.

4. Maxwell LJ, Zochling J, Boonen A, *et al.* TNF-alpha inhibitors for ankylosing spondylitis. *Cochrane Database Syst Rev* 2015; 14: CD005468.

5. van der Heijde D, Dijkmans B, Geusens P, *et al.* Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005; 52: 582–591.

6. van der Heijde D, Kivitz A, Schiff MH, *et al.* Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006; 54: 2136–2146.

7. Haibel H, Rudwaleit M, Listing J, *et al.* Efficacy of adalimumab in the treatment of axial spondyloarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. *Arthritis Rheum* 2008; 58: 1981–1991.

8. Sieper J, van der Heijde D, Dougados M, *et al.* Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis* 2013; 72: 815–822.

9. van der Heijde D, Schiff MH, Sieper J, *et al.* Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. *Ann Rheum Dis* 2009; 68: 922–929.

10. Davis JC Jr, Revicki D, van der Heijde DM, *et al*. Health-related quality of life outcomes in patients with active ankylosing spondylitis treated with adalimumab: results from a randomized controlled study. *Arthritis Rheum* 2007; 57: 1050–1057.

11. López-Medina C, Garrido-Castro JL, Castro-Jiménez J, *et al*. Evaluation of quality of life in patients with axial spondyloarthritis and its association with disease activity, functionality, mobility, and structural damage. *Clin Rheumatol* 2018; 37: 1581–1588.

12. van der Heijde D, Breban M, Halter D, *et al*. Maintenance of improvement in spinal mobility, physical function and quality of life in patients with ankylosing spondylitis after 5 years in a clinical trial of adalimumab. *Rheumatology (Oxford)* 2015; 54: 1210–1219.

13. Akkoc N, Can G, D'Angelo S, *et al*. Therapies of early, advanced, and late onset forms of axial spondyloarthritis, and the need for treat to target strategies. *Curr Rheumatol Rep* 2017; 19: 8.

14. Baraliakos X, Gensler LS, D'Angelo S, *et al*. Biologic therapy and spinal radiographic progression in patients with axial spondyloarthritis: a structured literature review. *Ther Adv Musculoskelet Dis* 2020; 12: 1759720X20906040.

15. Poddubnyy D, Listing J, Haibel H, *et al*. Functional relevance of radiographic spinal progression in axial spondyloarthritis: results from the GErman SPondyloarthritis Inception Cohort. *Rheumatology* 2018; 57: 703–711.

16. Danve A and Deodhar A. Treat to target in axial spondyloarthritis: what are the issues. *Curr Rheumatol Rep* 2017; 19: 22.

17. Fragoulis GE and Siebert S. Treatment strategies in axial spondyloarthritis: what, when and how? *Rheumatology* 2020; 59: iv79–iv89.

18. Robinson PC and Brown MA. The window of opportunity: a relevant concept for axial spondyloarthritis. *Arthritis Res Ther* 2014; 16: 109.

19. Dubash S, McGonagle D and Marzo-Ortega H. New advances in the understanding and treatment of axial spondyloarthritis: from chance to choice. *Ther Adv Chronic Dis* 2018; 9: 77–87.

20. Furst DE and Louie JS. Targeting inflammatory pathways in axial spondyloarthritis. *Arthritis Res Ther* 2019; 21: 135.

21. Mease P. Emerging immunomodulatory therapies and new treatment paradigms for axial spondyloarthritis. *Curr Rheumatol Rep* 2019; 21: 35.

22. Rudwaleit M, Schwarzlose S, Hilgert ES, *et al*. MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. *Ann Rheum Dis* 2008; 67: 1276–1281.

23. Sieper J, Lenaerts J, Wollenhaupt J, *et al*. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1. *Ann Rheum Dis* 2014; 73: 101–107.

24. Song I-H, Althoff CE, Haibel H, *et al*. Frequency and duration of drug-free remission after 1 year of treatment with etanercept versus sulfasalazine in early axial spondyloarthritis: 2 year data of the ESTHER trial. *Ann Rheum Dis* 2012; 71: 1212–1215.

25. Molto A, López-Medina C, van den Bosch FE, *et al*. Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial. *Ann Rheum Dis* 2021; 80: 1436–1444.

26. Haroon N, Inman RD, Learch TJ, *et al*. The impact of tumor necrosis factor α inhibitors on radiographic progression in ankylosing spondylitis. *Arthritis Rheum* 2013; 65: 2645–2654.

27. Jones GT, Dean LE, Pathan E, *et al*. Real-world evidence of TNF inhibition in axial spondyloarthritis: can we generalise the results from clinical trials. *Ann Rheum Dis* 2020; 79: 914–919.

28. Proft F and Poddubnyy D. Ankylosing spondylitis and axial spondyloarthritis: recent insights and impact of new classification criteria. *Ther Adv Musculoskelet Dis* 2018; 10: 129–139.

29. Machado P, Landewé R, Lie E, *et al*. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis* 2011; 70: 47–53.

30. Garrett S, Jenkinson T, Kennedy LG, *et al*. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994; 21: 2286–2291.

31. Calin A, Garrett S, Whitelock H, *et al*. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994; 21: 2281–2285.

32. Balestroni G and Bertolotti G. L'EuroQol-5D (EQ-5D): uno strumento per la misura della qualità della vita [EuroQol-5D (EQ-5D): an instrument for measuring quality of life]. *Monaldi Arch Chest Dis* 2012; 78: 155–159.

33. Klein JP, Logan B, Harhoff M, *et al*. Analyzing survival curves at a fixed point in time. *Stat Med* 2007; 26: 4505–4519.

34. Aletaha D, Maa J-F, Chen S, *et al*. Effect of disease duration and prior disease-modifying antirheumatic drug use on treatment outcomes in patients with rheumatoid arthritis. *Ann Rheum Dis* 2019; 78: 1609–1615.

35. Carron P, Varkas G, Renson T, *et al*. High rate of drug-free remission after induction therapy with golimumab in early peripheral spondyloarthritis. *Arthritis Rheumatol* 2018; 70: 1769–1777.

36. Coates LC, Moverley AR, McParland L, *et al*. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet* 2015; 386: 2489–2498.

37. Grigor C, Capell H, Stirling A, *et al*. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004; 364: 263–269.

38. Davis JC, Dougados M, Braun J, *et al*. Definition of disease duration in ankylosing spondylitis: reassessing the concept. *Ann Rheum Dis* 2006; 65: 1518–1520.

39. Feldtkeller E and Erlendsson J. Definition of disease duration in ankylosing spondylitis. *Rheumatol Int* 2008; 28: 693–696.

40. Barkham N, Keen HI, Coates LC, *et al*. Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. *Arthritis Rheum* 2009; 60: 946–954.

41. Song IH, Hermann K, Haibel H, *et al*. Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. *Ann Rheum Dis* 2011; 70: 590–596.

42. Dougados M, van der Heijde D, Tsai WC, *et al*. Relationship between disease activity status or clinical response and patient-reported outcomes in patients with non-radiographic axial spondyloarthritis: 104-week results from the randomized controlled EMBARK study. *Health Qual Life Outcomes* 2020; 18: 4.

43. Imkamp M, Lima Passos V, Boonen A, *et al*. Uncovering the heterogeneity of disease impact in axial spondyloarthritis: bivariate trajectories of disease activity and quality of life. *RMD Open* 2018; 4: e000755.

44. Macfarlane GJ, Rotariu O, Jones GT, *et al*. Determining factors related to poor quality of life in patients with axial spondyloarthritis: results from the British Society for Rheumatology Biologics Register (BSRBR-AS). *Ann Rheum Dis* 2020; 79: 202–208.

45. Mease PJ, Heijde DV, Karki C, *et al*. Characterization of patients with ankylosing spondylitis and nonradiographic axial spondyloarthritis in the US-based Corrona Registry. *Arthritis Care Res (Hoboken)* 2018; 70: 1661–1670.

46. Rudwaleit M, Claudepierre P, Wordsworth P, *et al*. Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. *J Rheumatol* 2009; 36: 801–808.

47. Sieper J, Landewé R, Magrey M, *et al*. Predictors of remission in patients with non-radiographic axial spondyloarthritis receiving open-label adalimumab in the ABILITY-3 study. *RMD Open* 2019; 5: e000917.

48. Vastesaeger N, van der Heijde D, Inman RD, *et al*. Predicting the outcome of ankylosing spondylitis therapy. *Ann Rheum Dis* 2011; 70: 973–981.

49. Glintborg B, Sørensen IJ, Østergaard M, *et al*. Ankylosing spondylitis versus nonradiographic axial spondyloarthritis: comparison of tumor necrosis factor inhibitor effectiveness and effect of HLA-B27 status. An observational cohort study from the nationwide DANBIO registry. *J Rheumatol* 2017; 44: 59–69.

50. Macfarlane GJ, Pathan E, Jones GT, *et al*. Predicting response to anti-TNFα therapy among patients with axial spondyloarthritis (axSpA): results from BSRBR-AS. *Rheumatology* 2020; 59: 2481–2490.

51. Arends S, van der Veer E, Kamps FB, *et al*. Patient-tailored dose reduction of TNF-α blocking agents in ankylosing spondylitis patients with stable low disease activity in daily clinical practice. *Clin Exp Rheumatol* 2015; 33: 174–180.

52. Rudwaleit M, Listing J, Brandt J, *et al*. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. *Ann Rheum Dis* 2004; 63: 665–670.

53. Machado PM and Deodhar A. Treat-to-target in axial spondyloarthritis: gold standard or fools' gold? *Curr Opin Rheumatol* 2019; 31: 344–348.

54. Arends S, Brouwer E, van der Veer E, *et al*. Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. *Arthritis Res Ther* 2011; 13: R94.

55. Poddubnyy D and Sieper J. Treatment of axial spondyloarthritis: what does the future hold? *Curr Rheumatol Rep* 2020; 22: 47.

Visit SAGE journals online
journals.sagepub.com/
home/tab

§SAGE journals