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ORIGINAL RESEARCH

Short-term response in new users of anti-TNF predicts long-term productivity and non-disability: analysis of Czech ATTRA ankylosing spondylitis biologic registry

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ABSTRACT

Objectives: To assess the role of short-term response to first anti-TNF in long-term prediction of disability.
Methods: In nationwide registry ATTRA, we identified ankylosing spondylitis patients starting anti-TNF between 01/2003 and 12/2016. Full disability and work impairment (WI; WPAI questionnaire) were predicted via the Cox- and lagged-parameter mixed-effect regression.
Results: 2,274 biologicals-naïve patients newly indicated to anti-TNF were prospectively followed (6,333 patient-years; median follow-up 1.9 years). Reaching BASDAI < 4 (77.4%) and ASDAS-CRP < 2.1 (61.1%) after 3 months of anti-TNF both decreased the risk of future disability by ≈2.5-fold. ASDAS-CRP < 2.1 predicted non-disability better than BASDAI < 4 & CRP < 5 mg/L ($p = 0.032$). BASDAI < 4 & CRP < 5 mg/L was comparable to BASDAI < 4 ($p = 0.941$) and to BASDAI change by >50% or by >2 points ($p = 0.902$). ASDAS-CRP change >1.1 and >2.0 both failed to predict non-disability. Once on anti-TNF therapy, the strongest predictor of WI was Pain (SF36). Yearly increase in indirect costs remains below €3,000 in those reaching ASDAS-CRP < 2.1.
Conclusions: Low disease activity measured by ASDAS-CRP ≤ 2.1 should be used to measure the outcome of new anti-TNF therapy. Continuous WI could be decreased through pain management.

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Ankylosing spondylitis; BASDAI; ASDAS; anti-TNF; work impairment; disability; predictive power; multivariate modeling

1. Introduction

Ankylosing spondylitis (AS) is a chronic autoimmune rheumatic disease affecting 0.1% to 1.4% of the population [1,2]. AS affects the sacroiliac joints, spine, and entheses but peripheral joints and extra-articular structures may also be involved. It is characterized by morphological changes including marginal vertebral body erosions, the formation of syndesmophytes, ossification of spinal ligaments, and, over time may result in a complete fusion of the spine.

Active disease largely impacts the patient´s health-related quality of life (QoL) [3,4] mostly through functional limitations [5–7] and pain [8]. From an economic perspective, higher disease activity generates higher disease-related costs [7,9,10] mainly due to productivity loss [5–7,11–13]. There are two main causes of productivity loss in AS: (1) Inflammatory flares triggering temporary drops in physical ability [14] resulting in episodic work impairment (WI) [6,7,9,10,15] and (2) constant background inflammation, which elicits gradual and irreversible damage to the musculoskeletal system [14] ultimately shortening the amount of time the patient is able to work (complete disability). Without effective management, patient prospects include increasing numbers of sick leaves, progressive pain [8], stiffness [14], and fatigue [16] until the patient ends-up struggling with common day-to-day tasks. Even if well-treated, disability ultimately affects up to 30% of all AS patients [17], so, from the AS patient as well as the societal perspective, preservation of social participation [14] and work capacity [6,18] are priorities. With a typical onset during the first half of productive life, AS has a devastating impact on patient life and produces a significant economic burden on society.

To prevent withdrawal from the labor force, both disease activity and the subjective symptoms need to be addressed [14,19]. Remission is now widely accepted as the primary goal in the management of AS. Low disease activity is seen as an alternative treatment target [14,19]. There is clear evidence that anti-TNF agents [2] improve AS symptoms including pain, and that they decrease AS–related productivity loss [17]. A stable remission, however, can be achieved only through early [20] and continuous [21] usage which generates substantial life-long costs [12]. It also seems that anti-TNF agents do not delay the gradual changes, i.e. radiographic progression [22], and thus cannot help regain work capacity [23].

Several predictors of WI and disability have been identified in bio-naïve populations [5,9,10,18,24–27], yet, the driving risk factors might well be different during anti-TNF therapy [16]. The latest international recommendations (2017's [14] and 2018's [28])

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The supplementary data for this article can be accessed here.

including recent European Medicines Agency's (EMA) Committee for Human Medicinal Products (CHMP) guidelines [1] emphasize two specific composite indexes with cut-off points to classify the disease activity and to measure the response to treatment. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [29] and Ankylosing Spondylitis Disease Activity Score (ASDAS) [30] were primarily developed as outcome measures [31]. Naturally, both also started to be used to establish patient prognoses. Still, there remains some controversy about their validity [32] and no studies have addressed their predictive power in the context of productivity loss in anti-TNF populations.

Our goal is to examine the prognostic value [31] of BASDAI, C-reactive protein (CRP) and ASDAS-CRP in the prediction of disability and WI in AS patients newly indicated for anti-TNF agent.

2. Methods

This is an analysis from a prospective observational longitudinal cohort study following bio-naïve incident users of anti-TNF agents. We predict complete disability by patient´s response to treatment after 3 months following initiation of the therapy. In working patients over time, we predict continuous WI using parameters from the preceding visit. The estimated productivity loss is monetized.

2.1. ATTRA registry

ATTRA is the nationwide Czech registry of rheumatologic patients treated with biological therapy. It is supported by the Czech Ministry of Health, jointly sponsored by pharmaceutical companies, managed by a steering committee and academically independent. The registry has been maintained since 2002 under the surveillance of the Czech Society of Rheumatology (CRS) and includes over 35 centers. Primary purpose of the project ATTRA is continuous evaluation of the effectiveness/efficacy and safety of biological therapy. Since 2003, ATTRA-AS has collected data on ≈95% of Czech AS patients treated with anti-TNF [33]. Patients are eligible after meeting the criteria of the CRS for treatment with anti-TNF drugs.[1] The selection of this particular agent remains at the discretion of the treating physician and the patient. Of all patients, 36.2%, 23.4%, 18.7%, 18.0%, and 3.7% were started on adalimumab, etanercept, golimumab, infliximab, and certolizumab, respectively. The agents were selected based on the summary of product characteristics and indication criteria for reimbursement given by the State Institute for Drug Control (adults, active disease with severe axial symptoms, increased serological inflammatory markers, inadequate therapeutic response to conventional therapy). These agents are included in the ´jumbo cluster´ group being subject to equal maximum daily reimbursement price. Drug switches were not considered for the purpose of the present study.

2.2. Measures of disease activity

Parameters in ATTRA-AS were recorded according to the EULAR expert group [34]. Per protocol, appointments are organized at 0-3-6-12-18-24-30-36-48-60-month intervals and then once a year. Importantly, ASDAS had been included in ATTRA since 2012 which results in lower number of observations available.

Using the OMERACT 10 [35] criteria, clinically important improvement and major improvement were represented by ASDAS-CRP cut-offs 1.1 and 2 points, respectively. A 'Good response' to anti-TNF therapy based on CRS [36] and NICE [37] was measured using a BASDAI reduction to 50% of the pre-treatment value or by 2 or more units. ASDAS-CRP below 2.1, which is considered equivalent to a BASDAI below 4 and plasma CRP below 5 mg/L, indicates low activity of the disease [36–38].

See online Supplementary material 1 for the remaining parameters.

2.3. Work impairment, disability, and costs

Complete disability status is granted based on physician/rheumatologist assessment which is required by the Czech Social Security Administration and consequently evaluated by the department of physicians/experts; then it was reported by the patient directly to ATTRA-AS. There was a major revision of the Czech disability pension scheme in 2010. Unlike the older two-stage system, disability is now classified into three stages: the first stage is defined by law as a decrease in working productivity by 35–49%, the second stage by 50–69%, and the third stage by 70–100%. Consequently, the incidence rate of allocation of full disability (third stage) dropped from 228.0 per 100,000 (a 7-year point-estimate from 2003 to 2009) to 93.2 (2010–2016). We used a weighted mean of 160.6 per 100,000 from the entire period of data collection (2003–2016).

We addressed limitations in both working and leisure time activities (WI and activity impairment (AI)) with Work Productivity and Activity Impairment (WPAI) questionnaire tailored to AS [39]. WI was monetized using the Human Capital Approach (HCA; 12 × WI × average monthly wage) using 2017´s average gross wage of €1493 (including all taxes paid) [40].

2.4. Survival analysis

Differences at baseline were assessed using Mann–Whitney test with ties and risk ratio (RR). We used disease activity after the initial 3 months of the therapy to predict the patient's full disability using the Cox-regression. Anonymized patient number (ID) was used to identify patients-at-risk, the first occurring full disability pension was set as ´event´ and calendar date of the appointment as unit of time-at-risk. Wherever stated ´adjusted´, we rounded up the usual suspects, i.e. age at anti-TNF initiation, baseline disease duration, and gender. Test of proportional-hazard assumption was done based on Schoenfeld residuals. The consistency of survival statistics was verified by plotting the Kaplan–Meier curve and the hazard function (not presented). The predictive power of the coefficients is expressed using Harrell's C-Index developed by Newson [41]. Briefly, C-Index represents a conditional probability that the ´survivor´ has the lower HR plus half the negligible probability that the two subjects have equal HR. C-Index in survival models was calculated using a 10% semi-random test sample stratified per baseline HAQ into 10 strata.

We a priori determined the linear Wald test of C-Index indexes to assess inequality in the predictive power of threshold values recommended for BASDAI and ASDAS-CRP [41]. Results with p-values < 0.05 were considered as statistically significant. Hence, this test was not burdened by previous multiple testing.

2.5. Linear regression

We used all collected parameters to predict WI using a clustered mixed-effect linear regression [31,42]. Parameters with p < 0.0001 were additionally lagged by 1 visit to allow for a temporal relationship providing the estimate as follows:

predicted WI_t = constant term + $\beta \times predictor_{it-1} + b_i + \varepsilon_{ij}$,

where *i* identifies a particular patient, *t* is the time of measurement, b_i is zero-mean random intercept for *i*-th patient, and e_{ij} are uncorrelated random errors.

The fit and validity were assessed using the adjusted Bryk/Raudenbush determination coefficient (R^2) [43], the Akaike information criterion (AIC), the mean squared error (MSE) of an estimator and robust standard errors to correct for heteroscedasticity. Collinearity was checked using variance inflation factors (package collin, Stata). An external cross-validation of the predicted coefficients was done based on 10% random sample withdrawn from the cohort. Result for the mixed models is presented using R^2 and MSE [44].

2.6. Data handling and reporting standards

ATTRA-AS meets the requirements of the European League Against Rheumatism (EULAR) recommendation [34] summarized in Protocol/user manual. Summary statistics are run on a weekly basis. Regular data validation is run on the level of automated queries and 3-monthly global reports complemented by ad hoc audits. All investigators are regularly trained. The data controller Institute of Biostatistics and Analyses Ltd. is certified ISO 20000–1:2006, ISO 9001:2001/2009 and ISO 27001:2006. There was no imputation done for missing values. We report in consensus with TRIPOD [31], STROBE [45] and RECORD [46] statements. All statistics were conducted using STATA 13.1 software, StataCorp LP, USA.

3. Results

3.1. Identification of the study population

We identified all bio-naïve AS patients newly initiating anti-TNF therapy between January 2003 and December 2016. Anti-TNF was initiated in a total of 2,274 AS patients. The follow-up was done until 2016; thus, ≈50% patients completed nine appointments (median follow-up of 1.9 years). Of total 17,033 appointments, we analyzed a set of 6,333 patient-years (13,991 times (visits)-at-risk[2]) with a total of 138 cases of all-cause complete disability (Figure 1). The incidence rate of newly allocated full disability pensions

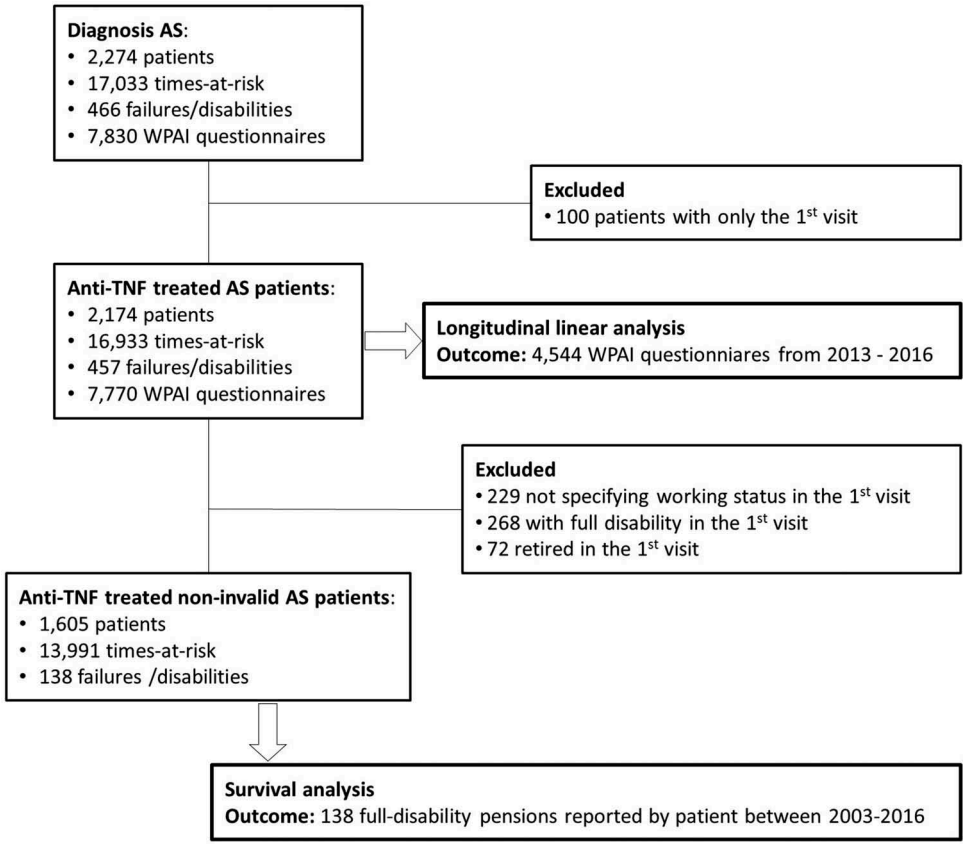

Figure 1. Study flowchart.

All incident users of anti-TNF included in the ATTRA-AS registry between 2003 and 2016 were followed until 2016. Between 2013 and 2016, 4,544 WPAI questionnaires were collected and used for the longitudinal analysis of WI. In the survival analysis, we used data from 1605 patients with 138 cases of new full disability pension allocated between 2003 and 2016.

2.2% (95% CI: 1.8%; 2.6%) was 13.7-fold above the average reported in the Czech general population in the respective years [47]. No difference in the disability rate was found between males and females (p = 0.480). None of the disabled had recovered working capacity during the follow-up period, yet, ATTRA-AS had been including significantly fewer disabled patients over time (Table 1).

3.2. Description of the population at baseline and after 3 months of anti-TNF therapy

Characteristics of the bio-naïve population along with their improvement after the initial 3 months of anti-TNF (Table 1) show that all parameters improved significantly. Notably, the QoL (EQ-5D) more than doubled from the initial value of 0.305 to 0.685 (Δ 0.380). Alleviation of pain (SF36) was reached in 87.3% patients.

Prior to anti-TNF, the estimated average yearly indirect costs from WI equaled to €9,585.[4] Anti-TNF significantly decreased WI, mostly through a reduction in presenteeism (i.e. coming to work despite illness, injury, etc., which often leads to reduced productivity at work), which dropped in 78.2% of the patients by ≈50%. Monetized using the HCA, this represented an average yearly reduction in the indirect costs by €4,586.

Most parameters differentiated the fully disabled (11.8%) from the remainder of the cohort (see online Supplementary Table 1). They failed on higher numbers of previous treatment lines and, after the initiation of anti-TNF, there were significantly more non-responders among the initially disabled. Compared to the rest of patients, their relative risk for CRP ≥ 5 mg/L, BASDAI ≥ 4 and ASDAS-CRP ≥ 2.1 after 3 months of anti-TNF were 1.39 (1.11; 1.75), 1.94 (1.66; 2.27) and 2.40 (1.58; 3.64), respectively. Moreover, disabled in the baseline or those with a high baseline WI (prior to anti-TNF) were less likely to experience improvement in pain (SF36; p < 0.001), irrespective of disease activity and stage[5].

3.3. Testing of BASDAI and ASDAS-CRP thresholds

HR of full disability for recommended threshold values was calculated using the Cox regression and cross-validated using the C-index. See online Supplementary table 3 for the characteristics of

Table 1. Characteristics of the entire cohort (2,274).

Entire cohort at baseline including the disabled (2,274 patients)				
Parameter	Mean ± SD or %	n	Improved after 3 months	Mean improvement ± (SD)
Age at anti-TNF initiation (years)	39.3 ± 11.1	2,274		
Male	72.8%	1,656		
Duration of disease (years)	7.9 ± 7.8	2,241		
Anti-TNF initiation after 2009	55.8%	1270		
Radiological stage (0–5)	3.1 ± 1.3	2,244		
Number of DMARDs prior to anti-TNF	0.9 ± 0.8	2,220		
Weight (kg)	79.5 ± 15.9	2,207		
Baseline ASDAS-CRP	4.0 ± 0.8	1,009	96.7%	Δ 2.0 ± 1.1
Baseline ASDAS-CRP > 2.1	99.3%	2257		
ASDAS-CRP in visit 2 < 1.3	31.2%	269		
ASDAS-CRP in visit 2 < 2.1	61.1%	526		
ASDAS-CRP in visit 2 < 3.5	93.8%	808		
Δ ASDAS-CRP in visit 2 ≥ 1.1	69.7%	618		
Δ ASDAS-CRP in visit 2 ≥ 2.0	43.7%	388		
Baseline CRP (mg/L)	26.1 ± 23.3	2,241	91.3%	Δ 20.0 ± 23.0
Baseline CRP ≥ 5 mg/L	88.5%	2,012		
Visit 2 CRP ≥ 5 mg/L	25.6%	582		
Baseline BASFI	5.3 ± 2.2	1,976	85.9%	Δ 2.2 ± 2.2
Baseline BASDAI	6.3 ± 1.7	1,933	93.6%	Δ 3.5 ± 2.3
Baseline BASDA I ≥ 4	94.0%	2,138		
Visit 2 BASDAI ≥ 4	22.6%	627		
Δ BASDAI by 50% in visit 2	45.1%	1,026		
Δ BASDAI by 2 in visit 2	89.3%	1,724		
Baseline HAQ	1.11 ± 0.53	2,116	77.3%	Δ 0.43 ± 0.48
Baseline SF36 Ph. functioning	46.9 ± 21.8	2,081	79.4%	Δ 20.2 ± 21.9
Baseline SF36 Role physical	21.5 ± 30.1	2,081	60.9%	Δ 32.1 ± 39.8
Baseline SF36 Pain	29.0 ± 15.7	2,081	87.3%	Δ 32.0 ± 24.5
Baseline SF36 Gen. health	31.3 ± 17.5	2,081	77.9%	Δ 16.0 ± 18.5
Baseline SF36 Vitality	32.6 ± 17.3	2,081	81.1%	Δ 21.6 ± 20.7
Baseline SF36 Social	46.4 ± 23.1	2,081	73.9%	Δ 24.7 ± 26.9
Baseline SF36 Emotional	55.4 ± 40.4	2,081	43.6%	Δ 20.3 ± 41.6
Baseline SF36 Mental	56.8 ± 18.4	2,081	73.9%	Δ 14.2 ± 17.9
EQ-5D	0.305 ± 0.304	2,115	86.0%	Δ 0.380 ± 0.350
Fully disabled[3]	11.8%	268	0.0%	
Working	65.1%	1,480	0.0%	
Not specified	10.1%	229		
Absenteeism %	11.5 ± 27.4	726	21.4%	Δ 6.1 ± 24.8
Presenteeism %	51.9 ± 21.8	651	78.2%	Δ 25.0 ± 24.3
WI %	53.5 ± 22.2	651	79.3%	Δ 25.6 ± 24.8
Activity Impairment	59.9 ± 21.6	1,031	80.3%	Δ 27.0 ± 25.3

Cross-sectional averages are complemented with the proportion of patients that improved after the initial 3 months of therapy. In continuous variables, n refers to the mean number of available records and, with regard to categorical variables, n refers to the number of patients in the respective category. % is calculated for each parameter based on non-missing values.

the patients entering the survival analysis and Supplementary table 4 and Supplementary table 5 for the complete list of HRs in all collected parameters.

BASDAI ≥ 4 and an ASDAS-CRP ≥ 2.1 measured prior to the anti-TNF initiation fail to foresee the disability (not presented). When measured after 3 months of anti-TNF therapy, all targets predict comparable hazard: approximately ≈ 2.5-fold higher chance of becoming fully disabled for those not reaching low disease activity (Figure 2). More specifically, patients not achieving treatment target defined as ASDAS-CRP < 2.1 have 2.776-fold higher risk of full disability compared to responders; similarly, patients having BASDAI ≥ 4 & CRP ≥ 5 mg/L have 2.354-fold higher risk. Albeit similar hazards, their predictive power differs importantly (Figure 3).

BASDAI ≥ 4 & CRP ≥ 5 mg/L performed comparably to the change (Δ) in BASDAI by <50% or by <2 points (p = 0.902) and to BASDAI omitting CRP (p = 0.941; Figure 3). ASDAS-CRP ≥ 2.1 predicted disability somehow better than BASDAI ≥ 4 & CRP ≥ 5 mg/L (p = 0.032). Δ ASDAS-CRP by <1.1 or <2.0 failed to foresee the disability and were largely outperformed by ASDAS-CRP ≥ 2.1.

We additionally tested thresholds of ASDAS-CRP ≥ 1.3 and 3.5 (inactive disease and high/very high disease activity). ASDAS-CRP ≥ 1.3 after the initial 3 months of anti-TNF provided an HR of 2.842 (95% CI: 1.098; 7.325) and C-index of 0.727 (95% CI: 0.555; 0.900). ASDAS-CRP ≥ 3.5 had HR of 2.958 (95% CI: 1.172; 7.463) and C-index of 0.725 (95% CI: 0.507; 0.944). We did not compare these measures with BASDAI since

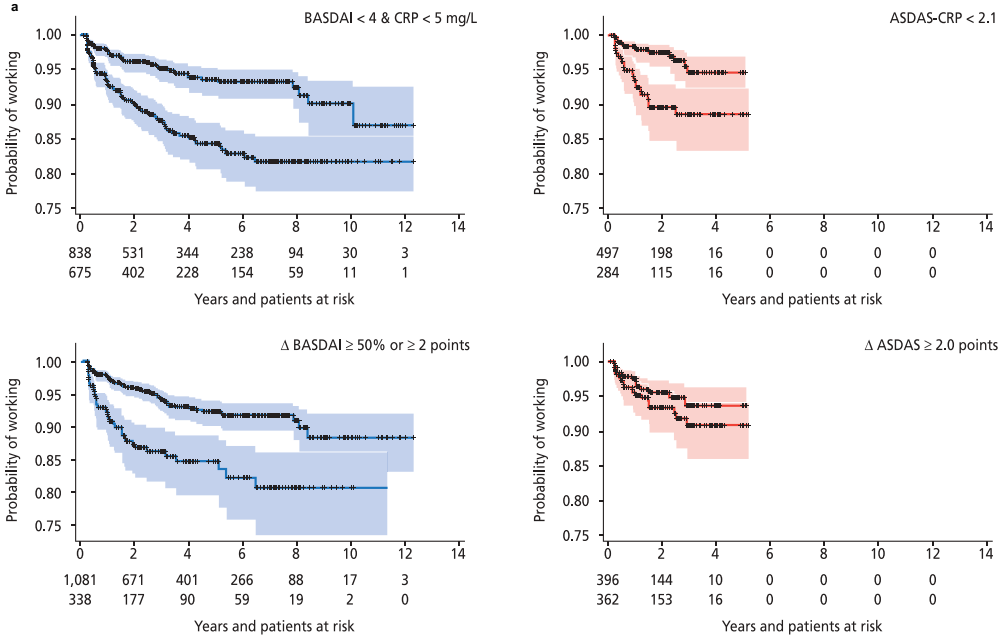

Figure 2. Censored Kaplan–Mayer survival estimates of newly allocated full disability pension along with 95% confidence intervals.

BASDAI, ASDAS, and CRP were measured after 3 months of anti-TNF therapy. The probability of employment (Y-axis) in patients at risk (X-axis) during the 14 years of follow-up (X-axis) is different in those reaching the therapeutic target value and patients adequately responding to therapy (i.e. with the minimal absolute change in disease activity (Δ)). Note that ASDAS started to be widely used in 2011; therefore, there were fewer observations available compared to BASDAI.

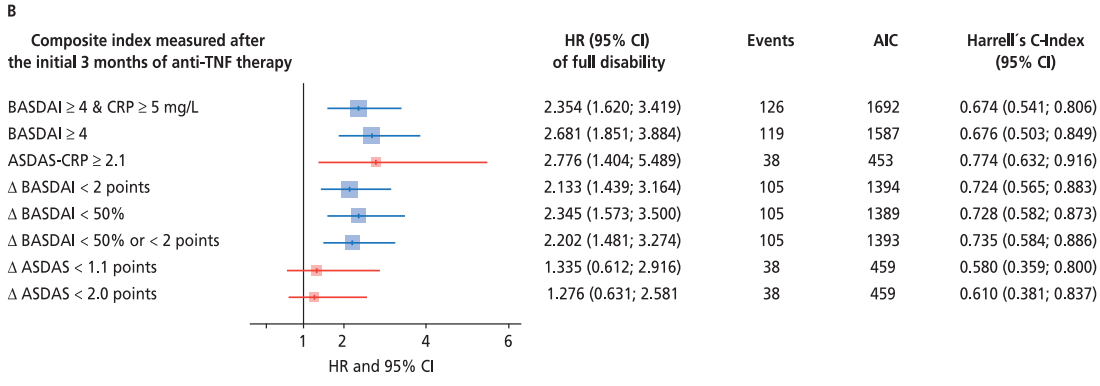

Figure 3. Comparison of the predictive performance of ASDAS-CRP, BASDAI, and BASDAI & CRP thresholds.

HR and 95% confidence intervals were calculated using the proportional-hazard Cox regression adjusted for baseline age and disease duration, calendar year at anti-TNF initiation and gender. Newly allocated disability pension was used as an event. Ties were handled according to Breslow [8]. C-Index was calculated using semi-random test sample stratified per HAQ into 10 strata. The size of each box corresponds to the relative sample size. Note that AICs-Akaike information criterion can be compared only for models with the same number of observations, i.e. ASDAS-CRP vs. ASDAS-CRP and BASDAI vs. BASDAI.

there are no analogous points for inactive disease or high disease activity in BASDAI.

Since ASDAS started to be used in 2011, there were fewer observations available compared to BASDAI. Comparing all measured characteristics of the working population prior to and after 2011, we found no potential confounding. In addition to sensitivity analysis, we rerun the regressions excluding patients who started anti-TNF therapy before 2010, 2011 or 2012. The results of the postestimation were confirmed (not presented).

Taken together, ASDAS-CRP´s threshold of 2.1 is the most predictive measure of the treatment target with respect to future invalidity.

3.4. Longitudinal exploratory analysis of continuous prediction of work impairment

Once on the anti-TNF therapy, the influence of collected parameters on the WI was explored via longitudinal one-level ID-clustered mixed-effect regression (for detailed patient characteristics see online Supplementary table 6). Important predictors ($p < 0.001$) were additionally lagged by 1 visit to allow for temporal causation. Models are adjusted to age and calendar year at anti-TNF initiation, gender, and baseline disease duration. In this exploratory part, the best 10 models are rated based on their power to predict observations in the test set (R^2).

BASDAI performed comparably to AI and qualified as the seventh best individual predictor of WI. ASDAS-CRP performed comparably to functional limitation measured with HAQ (Table 2). Unexpectedly, baseline CRP, disease duration, radiographic stage, and gender were not of significance relative to WI. The strongest predictor of WI was the pain domain of SF-36 questionnaire in which patients report on the symptoms experienced during the preceding month. Of note, pain predicts WI even when adjusted to disease activity (ASDAS-CRP, BASDAI) and functional limitations (BASFI, HAQ) with a $p < 0.001$ (coefficients not presented) meaning that the pain reported at given appointment is the best way of estimating how much the disease will affect patient productivity in the following 3 to 12 months.

We monetized the WI predicted by continuous disease activity using the average Czech wage (Figure 4). The histogram of the observed values of WI shows that most patients reached low disease activity defined as BASDAI < 4 or an ASDAS-CRP < 2.1. In these patients-responders, we predict the maximum increase in yearly indirect costs at €3,000.

4. Discussion

ATTRA-AS includes patients with higher disease activity and poorer QoL compared to the general AS patient population reported in a recent meta-analysis [3]. At inclusion between 2012 and 2016, the estimated average income loss was 3.2; 1.8; 1.6; and 1.1-fold higher than previously reported in patients from the Czech Republic, US, UK, and Western-EU, respectively [6,12]. Relative to a recent 22-nation survey [9], we report comparable numbers of working patients (65.1% vs. 62.7%) and comparably low baseline absenteeism (11.5% vs. 11.9%). Our results confirm that costs are driven by presenteeism.

Table 2. Continuous predictors of % work impairment (WI) in patients on anti-TNF therapy (n = 798; longitudinal exploratory analysis).

Lagged predictor (measured at the preceding visit)	Model 1	Model 2	Model 3	Model 6	Model 7	Model 8	Model 9	Model 10
SF36 Pain	−0.396 (−0.446; −0.347)							
SF36 Ph. Functioning		−0.444 (−0.502; −0.385)						
BASFI			4.320 (3.813; 4.825)					
WPAI Activity Imp				0.452 (0.410; 0.495)				
BASDAI					3.851 (3.353; 4.350)			
EQ5D						−24.8 (−28.9; −20.7)		
ASDAS-CRP							6.131 (5.196; 7.066)	
HAQ								16.258 (14.041; 18.476)
Constant term	85.1	99.2	14.7	22.6	24.8	31.2	19.9	42.5
Total observations	975	975	1,674	1,675	1,677	1,666	1,633	1,676
Clusters (IDs)	439	439	575	575	575	573	572	575
B/R R-squared Level 2	0.700	0.634	0.545	0.715	0.523	0.38	0.415	0.494
AIC	8,154	8,154	13,975	13,998	14,076	14,041	13,705	14,078
Test sample R-squared	0.520	0.480	0.440	0.400	0.395	0.330	0.310	0.299
Test sample MSE	0.020	0.024	0.026	0.026	0.028	0.035	0.030	0.030

Parameters lagged by 1 visit (to allow for temporal causation) were analyzed via mixed-effect regression clustered using patient ID. The best 10 models were adjusted for age and calendar year at anti-TNF therapy onset, gender, and baseline disease duration. External cross-validation represented by MSE and R2 was done using a random unstratified 10% test sample. Ninety-five percent confidence intervals are shown in brackets. Model 7 should be read as linear equation estimating WI = 24.8 (constant term) + 3.851 × BASDAI (measured on the preceding visit); Model 9 as WI = 19.9 (constant term) + 6.131 × ASDAS-CRP (measured on the preceding visit). More specifically, an increase in ASDAS-CRP by 1 point predicts an increase in WI by 6.131%; a 1-point increase in BASDAI predicts a 3.851% increase in WI. The strongest predictor of WI was Pain measured using SF36. Worsening of pain by 30% (by 30 points on 0 – 100 scale) predicts 11.88% (0.396 × 30) drop in work productivity, i.e. €1065 (€933; €1200) future raise in yearly indirect costs (Model 1).

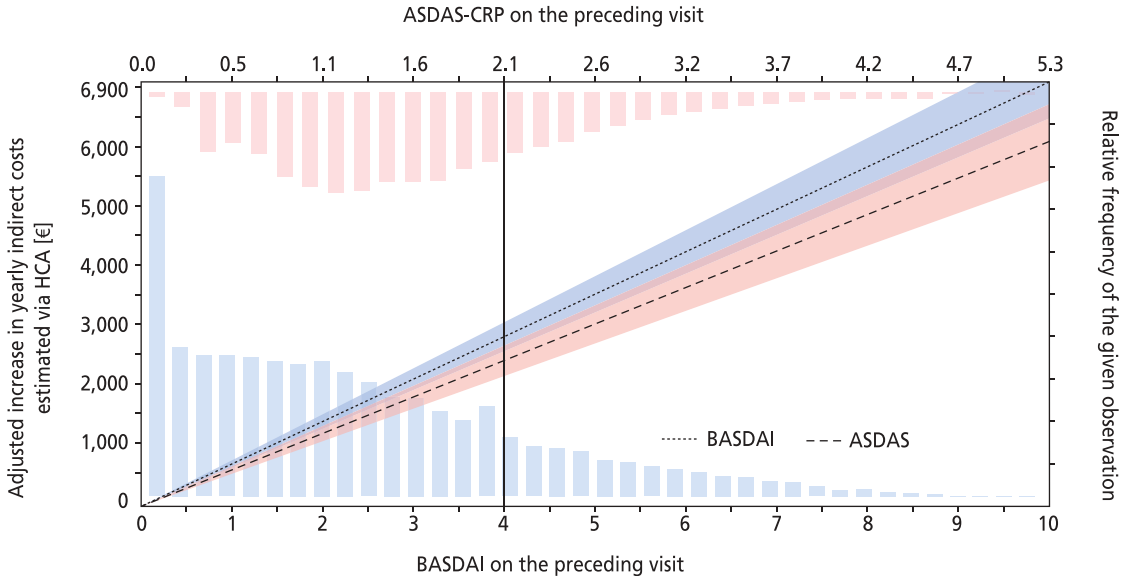

Figure 4. Linear prediction of the indirect costs foreseen by BASDAI and ASDAS as individual predictors.

Estimates from Models 7 (BASDAI, lower axis) and 9 (ASDAS-CRP, upper axis) were monetized via HCA: Yearly indirect costs = 12 × WI × average monthly wage (left-hand axis). The figure shows the increase in yearly costs; thus, the constant term is reduced. Estimates are accompanied by overlapping 95% confidence bands. The histogram shows the relative frequency of the individual disease activity states (right-hand axis). Most patients on anti-TNF therapy maintain low disease activity represented by threshold BASDAI < 4 and an ASDAS-CRP < 2.1 which holds predicted additional yearly indirect cost below ≈ €3,000

Approximately 80% patients respond to the therapy by reaching low disease activity. Despite more than 2-fold BASDAI at baseline, the incidence of disability (2003 to 2016) drops to what was previously observed in bio-naïve patients of a similar age and disease duration (2.2% vs. 2.5%) [48]. We found a 6-fold, 2-fold, 2-fold and 1.5-fold improvement in absenteeism, presenteeism, WI, AI compared to the anti-TNF treated patients recently reported from the British Register [17]. We confirm, however, that the complete disability is not reversible with anti-TNF therapy [23].

Although CRP predicts WI in bio-naïve patients [18,49], we show that only high CRP levels have prognostic potential during anti-TNF therapy. Consequently, the predictive power of BASDAI ≤ 4 is non-inferior to BASDAI ≤ 4 & CRP ≤ 5 mg/L. BASDAI alone delivers a good measure of both response to treatment and low disease activity after 3 months of anti-TNF. Unlike BASDAI, ASDAS-CRP captures the range of disease activity close to a normal distribution (Figure 4). It is an excellent pointwise predictor; nonetheless, there might be some concerns about the points chosen to indicate a response to treatment (Δ ASDAS ˂ 1.1 and 2.0). ASDAS-CRP ˂ 2.1 is the most reliable predictor of non-disability.

Disease activity prior to anti-TNF initiation, baseline disease duration, radiographic stage and gender do not predict WI and disability in AS patients once anti-TNF therapy started. During the therapy, we show the key influence of pain on the productivity.

The principal limitation of this study is that the ATTRA-AS cohort represents a specific subpopulation of AS patients with high baseline disease activity. We could not include a control population reflecting 'average' AS patients such as with lower baseline disease activity or AS patients treated solely on NSAIDs. Traditionally, the indication criteria for reimbursement given by the HTA authority are more selective than the clinical criteria indication for a given anti-TNF drug. In the real world, only a part of those in need have access to anti-TNF. There is a probability of confounding commonly referred to as ´selective prescribing´ [4,42,50] and any inferences drawn should be done so with that in mind.

It has been previously shown that the type of job [24,51,52] and education level [47] were crucial factors for the development of AS-related productivity loss. Another shortcoming of our analysis is that we could not reflect this fact as this information is not collected in ATTRA. Also, the predicted indirect costs were calculated based on the average Czech wage, which might not reflect the real-world status of all patients with long-standing AS. Nevertheless, one can adapt our model by introducing a domestic wage into the formula shown in the Methods section.

The second aim of the presented study was to compare performance ASDAS and BASDAI to other continuous predictors; hence, the exploratory part (Table 2) is naturally burdened by multiple testing. In the survival analysis, we compared different measures of disease activity. We clearly distinguished hypothesis-testing with a-priori-determined outcomes, from test and significance levels confirming the non-equality between ASDAS and BASDAI.

5. Conclusions

The immediate response to the first anti-TNF drug largely determines patient long-term prospects. After the initial 3 months of anti-TNF therapy, BASDAI < 4 and ASDAS-CRP < 2.1 were reached by 77.4% and 61.1% patients. Of all BASDAI and ASDAS-CRP thresholds tested, low disease activity measured as ASDAS-CRP < 2.1 should be primarily used to measure the low disease activity of anti-TNF therapy since it best predicts patient long-term non-disability.

The yearly increase in indirect costs continuously predicted by disease activity remains below €3,000 in those reaching ASDAS-CRP < 2.1. The WI is most influenced by pain which should be monitored once reaching low disease activity.

Notes

1. Diagnosis of AS according to the modified New York or ASAS criteria; disease activity BASDAI ≥ 4 at two consecutive checkups in a period of at least 4 weeks; CRP > 10 mg/l; failure of conventional therapy in patients with polyarthritis (4 weeks of NSAIDs, 6 months of sulfasalazine); 1 glucocorticoid local injection for monoarthritis; positive expert opinion; absence of a contraindication for treatment [36].
2. Patients with partial disability (n = 66) were considered to remain at-risk of complete disability.
3. Stage 2 prior to 2010 and stage 3 after 2010.
4. Note that patients indicated for anti-TNF represent a specific subset, where advanced disease states were more prevalent compared to average AS patients.
5. Mann–Whitney test for absolute change adjusted for age and calendar year at anti-TNF therapy initiation, gender, baseline disease duration, and also disease activity and stage at visits 1 and 2 (using CRP, BASDAI and radiological staging). Baseline cohort characteristics stratified by radiological stage (0–5) are available as online Supplementary Table 2.

Author contributions

Jakub Závada managed the registry. Tomáš Doležal, Jiří Vencovský, and Karel Pavelka prepared the protocol for data extraction. Lucie Nekvindová, Zlatuše Křístková, Michal Svoboda, and Michal Uher had access to the registry and extracted the data for analysis according to the protocol. Jan Tužil, Tomáš Mlčoch, and Tomáš Doležal wrote the manuscript and Jan Tužil had primary responsibility for the final content. Jan Tužil designed the statistical analysis. Jan Tužil and Jitka Jirčíková prepared and analyzed the data. Lucie Nekvindová, Zlatuše Křístková, Michal Svoboda, and Michal Uher performed the statistical review, Tomáš Mlčoch performed the HTA review, Tomáš Doležal, Jakub Závada, and Karel Pavelka all worked on the continuous medical review of the manuscript.

Patient involvement

Patient consent with collection and processing of personal information was signed at the inclusion into the ATTRA-AS by each patient. Patients had the right to withdraw from the registry, for any reason, at any time. The handling of personal information followed Regulation (EU) 2016/679 and (CZ) Act No. 101/2000 Coll. Patients reported on their quality of life, disease burden, and work impairment at any visit during the interview with their treating physician and also via paper questionnaires. Patients are aware of the scientific purpose of the registry. The results of analyses from ATTRA are communicated via publications for both medical and lay public. More details on http://attra.registry.cz/index.php?pg=gdpr.

NCA and ethics approval

Project ATTRA was approved and is supervised by multicentric ethics committee and competent authority under the identifier 1011290000. All records are anonymized. Personal data include birth date, gender, and initials.

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Declaration of interest

K Pavelka has received honoraria for lectures and consultations from Roche, AbbVie, MSD, BMS, Pfizer, Biogen, and UCB. J Vencovský has received honoraria for lectures and consultations from AbbVie, Biogen, Eli Lilly, GSK, MSD, Novartis, Pfizer, Roche, Sanofi, UCB. J Závada has received honoraria for lectures and consultations from AbbVie, Elli-Lilly, BMS, Pfizer, Biogen, and UCB. There was no financial reward related to this article. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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