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Original article

Impact of tobacco smoking on response to tumour necrosis factor-alpha inhibitor treatment in patients with ankylosing spondylitis: results from the Danish nationwide DANBIO registry

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Abstract

Objectives. To investigate the association between tobacco smoking and disease activity, treatment adherence and treatment responses in patients with AS treated with their first tumour necrosis factor-alpha inhibitor (TNFi) therapy in routine care.

Methods. Observational cohort study based on the Danish nationwide DANBIO registry. Kaplan–Meier plots, Cox and logistic regression analyses by smoking status (current/never/previous) were calculated for treatment adherence and BASDAI 50%/20 mm-response. Additional stratified analyses were performed for gender and TNFi-type.

Results. Of 1576 AS patients included in the study, 1425(90%) had known smoking status (current/never/previous: 43%/41%/16%). The median follow-up time was 2.02 years (IQR 0.69–5.01). At baseline, current smokers compared with never smokers had longer disease duration (4 years (1–12)/2 years (0–10)), higher BASDAI (61 mm (47–73)/58 mm (44–70)), BASFI (53 mm (35–69)/46 mm (31–66)) and BASMI (40 mm (20–60)/30 mm (10–50)) scores (all $P < 0.01$). Current and previous smokers had shorter treatment adherence than never smokers (current: 2.30 years (1.81–2.79) (median (95% CI)); previous: 2.48 years (1.56–3.40), never: 4.12 years (3.29–4.95)), $P < 0.0001$). Similar results were found in multivariate analyses (current versus never smokers, HR 1.41 (95% CI 1.21–1.65), $P < 0.001$), most pronounced among men. Current smokers had poorer 6 months' BASDAI50%/20 mm-response rate than never smokers (42%/58%, $P <$ 0.001). In multivariate analyses, current smokers had lower odds of achieving

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BASDAI50%/20 mm-response than never smokers, both overall (OR 0.48 (95% CI 0.35–0.65), $P < 0.0001$) and for the different TNFi-types (adalimumab 0.45 (0.27–0.76)/etanercept 0.24 (0.10–0.61)/infliximab 0.57 (0.34–0.95)).

Conclusion. In this study of TNFi-treated AS patients in clinical practice, current and previous smokers had significantly poorer patient-reported outcomes at baseline, shorter treatment adherence and poorer treatment response compared with never smokers.

Key words: Ankylosing spondylitis, Smoking, Tumour necrosis factor-alpha inhibitors, Outcome, Routine care

Rheumatology key messages

- Current smoking was frequent among TNF inhibitor treated Danish patients with AS.
- Upon start of TNF inhibitor treatment, smokers with AS had higher disease activity than never smokers.
- In AS, smokers (current or previous) had poorer TNF inhibitor treatment response and adherence than never smokers.

Introduction

The introduction of TNF-α inhibitor (TNFi) treatment has improved outcomes in AS. Nevertheless, approximately half of the patients terminate treatment owing to side effects or lack of effect [1–4]. Several studies have aimed to identify effect modifiers and predictors of treatment response [5–7], but it has proven difficult to pinpoint the patients who are most likely to benefit from therapy [7].

Smoking is an important and potentially modifiable risk factor in axial spondyloarthritis (axSpA) and AS [8]. Current smokers seem to have poorer patient-reported outcomes, a higher disease activity [9–13] and a higher risk of progressive, structural damage compared with non-smokers [14, 15]. Studies on the impact of smoking on effectiveness of TNFi treatment in AS patients are few. In a recent Swiss study, current smokers with axSpA had poorer response rates compared with non-smokers in a real-life cohort treated with TNFi [16]. However, smoking did not modify health-related quality of life among TNFi-treated Australian AS patients [17]. Previous studies have reported a negative impact of smoking on the effectiveness of TNFi treatment in patients with RA [18–21] and PsA [22, 23].

The nationwide DANBIO registry includes clinical data on patients with rheumatic diseases treated with TNFi in routine care in Denmark [24, 25]. We have previously described demographics and clinical outcomes in patients with AS treated with TNFi [1]. The primary aim of the present study was to compare effectiveness in current smokers, previous smokers and never smokers regarding disease activity, treatment responses and adherence rates in patients with AS initiating their first TNFi therapy in routine care. The secondary aim was to study whether the impact of smoking was influenced by gender and TNFi type.

Methods

The DANBIO registry was initiated in the year 2000 and covers >90% of Danish adults suffering from rheumatic disease treated in routine care with biologics [24, 26]. According to Danish legislation, the registration and publication of data from clinical registries do not require patient consent or approval by ethics committees. Physicians are recommended to report data prospectively by an online system at least biannually and when medication is changed (www.danbio-online.dk).

Baseline demographics include smoking habits, age, gender, BMI, disease duration, current treatment with MTX or other conventional synthetic DMARDs (csDMARD). In addition to CRP level (normal range ⩽10 mg/l) and visual analogue scales (VASs) for scores of pain, patient's global, fatigue and physician's global assessments, the patient's functional status and disease activity are monitored by BASDAI, BASFI and BASMI, which are validated disease outcome measures in AS [27, 28]. By 1 January 2014, 1775 patients with a diagnosis of AS had been registered and treated with a biologic drug (bDMARD), according to the treating rheumatologist. We excluded patients treated with certolizumab pegol (n = 5) and bDMARDs other than TNFi (n = 12), patients participating in clinical trials (n = 140), patients not followed in DANBIO since the commencement of their first TNFi (n = 19) or with erroneous baseline registrations (n = 23), leaving 1576 patients in the study.

Tobacco smoking

Patients were divided into three groups according to smoking status: current (⩾1 cigarette/day), previous and never smokers. In previous smokers, the number of years since smoking cessation was recorded. Smokers who had stopped smoking the year they started TNFi were classified as previous smokers ($n = 25$). Queries were sent to the departments regarding patients with incomplete data on smoking status. A rheumatologist then obtained the information from the medical records or by asking the patients.

Treatment adherence

Treatment adherence was calculated as the number of years each patient maintained treatment. Start date was the date of the first given dose and stop date was the date

of the first missed dose. Temporary treatment interruptions (e.g. due to infections or surgery) of ⩽3 months' duration were allowed. All observations were censored by 1 September 2014. Among patients with no follow-up since June 2014, data were censored according to the last visit registered.

The reasons for drug discontinuation are registered in DANBIO in pre-specified categories: lack of effect, adverse events, disease remission, pregnancy, surgery, cancer, death, infections, loss to follow-up and other reasons. In the following, reasons for discontinuation are divided into three categories: adverse events (including infection, death or cancer), lack of effect and other (including pregnancy, surgery, loss to follow-up, remission and other reasons for discontinuation).

Treatment response

Disease activity was evaluated at baseline and after 3 and 6 months' therapy. The baseline visit was defined as a visit within the time frame that ranged from 60 days before until six days after initiation of therapy. For the 3 months' visit, the time frame was 10–17 weeks, and for the 6 months' visit the time frame was 18–32 weeks after treatment start. If more than one registration occurred within a given time frame for an individual patient, the registration closest to the given time-point was selected for analysis. If a patient had no registrations within a given time window, data were registered as missing for the given visit.

In accordance with international recommendations, clinical response was defined as achievement of either a 50% or a 20-mm reduction in BASDAI (BASDAI50%/20 mm response) [27, 28]. Arbitrarily and in agreement with previous studies, we classified patients as responders if they achieved clinical response (yes/no) at both the 3 and 6 months' visits compared with baseline. In the case of missing data at either the 3 or 6 months' visit, one registration of clinical response was sufficient to classify the patient as a responder. Patients who stopped treatment within the first 3 months of therapy were considered non-responders (n = 112). Response rates were calculated as the proportion of patients who achieved a BASDAI50%/20 mm response.

Statistics

Statistical analyses were performed by SPSS (version 20.0, SPSS Inc., Chicago, Illinois, USA). Demographic and descriptive data are presented by medians/interquartile ranges (IQRs). Groups were compared by non-parametric tests (χ^2, Kruskal–Wallis and Mann–Whitney tests). In all tests, P-values <0.05 were considered statistically significant. Calculations were based on observed data and no imputation of missing data was performed.

Kaplan–Meier plots and log rank tests were performed for analyses of treatment adherence for current, previous and never smokers. Additional testing was done in order to ensure that proportionality was present during the observation period (data not shown). We performed univariate and multivariate Cox regression analyses to study the impact of smoking on treatment adherence and calculated hazard ratios (HRs) for treatment discontinuation with time in study as the underlying time scale. Univariate and multivariate logistic regression analyses and odds ratios (ORs) were calculated to identify the impact of smoking (current/previous/never) on the achievement of clinical response. The following baseline factors were considered *a priori* as confounders and included in all multivariate analyses: age (in quartiles), gender, disease duration (in tertiles), calendar year of starting TNFi (in tertiles). Age, disease duration and year of treatment start were included as categorical variables to allow for possible non-linear effects. Baseline MTX use (yes/no) and TNFi type (adalimumab/etanercept/golimumab/infliximab) were considered potential confounders and were added one by one to the multivariate model, but were only included if they altered the OR/HR of smoking by >10%. Baseline VAS scores, CRP, BMI, BASDAI, BASFI and BASMI were considered intermediate variables between tobacco smoking and outcomes and not included in the main multivariate analyses. For sensitivity we performed multivariate logistic regression analyses (current *vs* never smokers) that besides the *a priori* confounders additionally included all the variables in which the baseline values differed significantly among current *vs* never smokers. The latter analysis was also performed where the confounding effect of all variables was adjusted for by use of propensity score. Stratified analyses were performed according to gender and TNFi type (adalimumab/etanercept/infliximab, but not for golimumab, owing to limited data).

Results

Characteristics at baseline

A total of 1576 bDMARD-naïve patients initiating treatment with adalimumab, etanercept, golimumab or infliximab as the first TNFi were included (Table 1). Among the 1425 patients (90%) with known smoking status, 43% were current, 41% never and 16% previous smokers, and 39% of women and 44% of men were current smokers. Patients with missing smoking status were more often men and were more often treated with golimumab, in contrast to patients with available smoking information (Table 1).

At baseline, current smokers had higher BASDAI, BASMI and BASFI scores compared with never smokers and had higher BASDAI, patient global and pain scores compared with previous smokers (Table 1). Previous smokers were older and had longer disease duration than current and never smokers. The reasons for stopping TNFi treatment were independent of smoking status (Table 1). Male current smokers had significantly higher BASDAI, BASFI, BASMI and physician global scores and a longer disease duration than male never smokers, whereas age, CRP, BMI, patient's pain, fatigue and global scores were similar (data not shown). Female current smokers had significantly higher BASFI and physician global scores than female never smokers, whereas age, BMI, disease

Table 1 Demographics and patient characteristics

	Smoking status					
	Current	Never	Previous	Current versus never P value[a]	Current versus previous P value[b]	Smoking status unknown
Baseline						
Number, n (%)	614 (39)	578 (37)	233 (15)	—	—	151 (10)
Age, median (IQR), years	41 (32–50)	39 (32–50)	48 (40–57)	0.3	<0.0001	41 (32–51)
Disease duration, median (IQR), years	4 (1–12)	2 (0–10)	9 (1–19)	0.01	0.003	3 (0–15)
Women, n (%)	161 (26)	192 (33)	57 (24)	0.008	0.6	32 (21)[c]
Body mass index, median (IQR), kg/m^2	25 (23–29)	26 (22–28)	26 (24–29)	0.4	0.1	25 (22–28)
TNFi drug type, n (%)						
Adalimumab	231 (38)	230 (40)	110 (47)	0.4	0.03	54 (36)[c]
Etanercept	104 (17)	107 (19)	42 (18)			21 (14)
Infliximab	231 (38)	193 (33)	74 (32)			49 (32)
Golimumab	48 (8)	48 (8)	7 (3)			27 (17)
TNFi start year, n (%)						
2000–04	81 (13)	68 (12)	25 (11)	0.4	0.2	23 (15)[c]
2005–09	335 (55)	302 (52)	122 (52)			61 (40)
2010–13	198 (32)	208 (36)	86 (37)			67 (44)
MTX use, n (%)	171 (28)	149 (26)	50 (31)	0.4	0.06	37 (25)
CRP, median (IQR), mg/l	13 (5–26)	10 (4–23)	10 (4–21)	0.07	0.8	13 (6–23)
BASDAI, median (IQR)	61 (47–73)	58 (44–70)	56 (41–69)	0.009	0.002	62 (44–71)
BASFI, median (IQR)	53 (35–69)	46 (31–66)	51 (33–69)	0.002	0.3	50 (36–70)
BASMI, median (IQR)	40 (20–60)	30 (10–50)	40 (20–60)	<0.0001	0.7	40 (15–50)
Patient global (0–100), median (IQR), mm	69 (52–82)	69 (49–83)	67 (46–79)	0.3	0.04	71 (52–84)
Patient pain (0–100), median (IQR), mm	67 (49–78)	65 (45–79)	62 (44–76)	0.3	0.02	65 (45–78)
Patient fatigue (0–100), median (IQR), mm	69 (51–82)	70 (46–81)	68 (46–77)	0.3	0.07	71 (56–84)
Physician global (0–100), median (IQR), mm	40 (25–58)	35 (22–49)	38 (21–55)	0.001	0.07	33 (21–47)
Stop reason, n (%)[d]						
Lack of efficacy	162 (40)	140 (44)	67 (46)	0.4	0.5	39 (46)
Adverse events	117 (29)	77 (24)	38 (26)			21 (25)
Other	117 (29)	88 (28)	40 (27)			24 (29)
Unknown	10 (2)	10 (3)	2 (1)			0 (0)
Changes at 3 months[e]						
Change in Patient global, median (IQR), mm	26 (6–48)	33 (16–59)	22 (7–43)	0.003	0.6	—
Change in Patient pain, median (IQR), mm	28 (8–49)	37 (13–55)	22 (7–46)	0.03	0.4	—
Change in Patient fatigue, median (IQR), mm	19 (2–38)	24 (6–51)	20 (2–33)	0.009	1.0	—
Change in BASDAI, median (IQR)	23 (7–41)	29 (14–45)	18 (9–35)	0.004	0.4	—
Change in BASFI, median (IQR)	14 (1–29)	18 (6–35)	12 (1–26)	0.005	0.6	—
Change in BASMI, median (IQR)	10 (0–20)	10 (0–20)	10 (0–20)	0.9	0.9	—

Baseline demographics, disease activity and reasons for terminating TNFi treatment, according to smoking status at the baseline visit (n = 1576) and changes in disease activity measures between baseline and 3 months' follow-up. [a]Mann–Whitney or χ^2. [b]Mann–Whitney or χ^2. [c]Significantly different ($P < 0.05$) compared with all patients with known smoking status. [d]Percentages of patients who have terminated treatment according to smoking status. [e]Change at three months compared with baseline, shown as decreases. Patients with available data at baseline (percentage/%): smoking (90), age (100), disease duration (89), gender (100), BMI (61), drug type (100), start year (100), MTX use y/n (100), CRP (75), BASDAI (76), BASFI (76), BASMI (65), patient global (69), pain (69), fatigue (58), physicians global (56). IQR: interquartile range; TNFi: TNF-α inhibitor; VAS: Visual Analogue Scale; n: number.

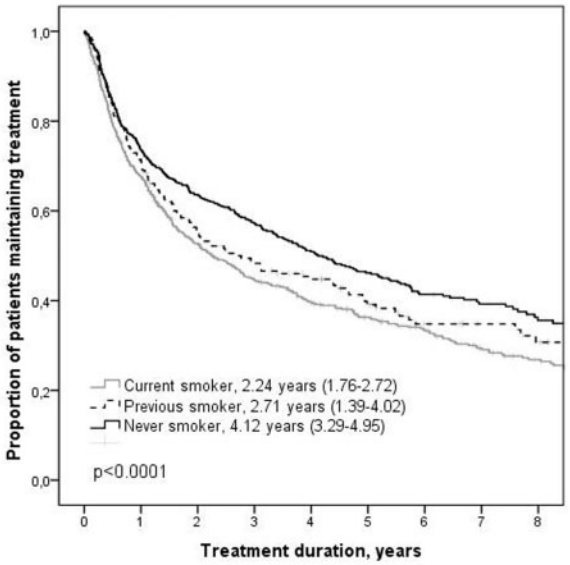
duration, patient's pain, fatigue and global scores, BASDAI and BASMI were similar (data not shown).

Treatment adherence

The total follow-up time was 5983 patient years, with a median follow-up time of 2.02 years (IQR 0.69–5.01). Current and previous smokers had poorer treatment adherence than never smokers (Fig. 1 and Table 2). The tendency was the same in stratified analyses according to gender, but the results reached statistical significance mainly in men (Table 2).

Among previous smokers, patients who had stopped smoking during the previous 5 years (n = 106) had similar drug survival to the patients who had stopped ⩾6 years previously (n = 111) (Kaplan–Meier, log rank P = 0.8). Patients with missing smoking data had similar treatment adherence to patients with known smoking status (log rank, P = 0.6).

FIG. 1 Treatment adherence according to smoking status—results from Kaplan–Meier analysis [median (95% CI)]



Treatment duration, years	0	1	2	3	4	5	6	7	8
Patients still treated, n	1425	983	739	593	482	367	274	196	140
Stopped treatment, n	0	26	68	57	52	73	61	60	40

Hazard ratios for withdrawal from univariate Cox regression analysis: current versus never smokers 1.32 (95% CI 1.14–1.53), previous versus never smokers 1.24 (1.02–1.50). n: number.

Treatment adherence was poorer among current *vs* never smokers in patients, regardless of type of TNF-inhibitor (Cox regression analyses, Table 3). Previous smokers had poorer treatment adherence than never smokers for adalimumab and etanercept (Table 3).

Disease activity and treatment response

Measures of disease activity had improved less in current smokers than in never smokers at 3 months' follow-up (Table 1). Similar tendencies were observed at 6 months for patient global, BASDAI and BASFI scores (data not shown). Both current and previous smokers had lower response rates than never smokers (Fig. 2).

Current and previous smokers had significantly lower odds of achieving response than never smokers, both overall and stratified according to gender (Table 4). For stratified analyses according to TNFi drug type, similar results were found among current versus never smokers for all three TNFi and a tendency of lower odds of response in previous smokers (Table 4).

A sensitivity analysis using multivariate regression including all the variables that differed among current *vs* never smokers at baseline (BASDAI, BASFI, BASMI, disease duration, VAS physician global) showed similar results (current *vs* never smokers, OR = 0.49 (95% CI 0.32–0.75, $P < 0.001$)). When the same covariates were adjusted for in the regression analysis as a propensity score, the results were unaltered (data not shown).

There was no statistically significant interaction between smoking and gender or between smoking and TNFi drug type (both $P > 0.05$ in Cox and logistic regression analyses).

Discussion

In this study of patients with AS who initiated treatment with the first TNFi in a real-life setting, more than half were current or previous smokers. At the start of treatment, current smokers had higher disease activity compared with never and previous smokers. Both current and previous smoking had a negative impact on treatment effectiveness and increased the risk of withdrawing from treatment. These findings are important, since smoking is potentially modifiable.

We found that current smokers had significantly higher BASMI, BASDAI and BASFI scores and a trend towards a higher CRP level at the start of TNFi treatment compared with never smokers. The negative impact of smoking on disease activity has previously been described in cross-sectional studies among patients with AS [9, 11–13, 29, 30]. In an English survey of 612 patients with established AS, smoking was associated with aggravation in patient-reported outcomes, including function, pain and quality of life [9]. Similar results have been reported in patients with early axSpA [10]. However, these studies included none or only low numbers of TNFi-treated patients [9–11, 29, 30]. The negative impact of smoking may be caused by increased systemic inflammation [29, 31]. accelerated radiographic progression [8, 14, 32, 33], decreased functional activity, reduced lung capacity, as well as comorbidities or socioeconomic challenges [9, 10, 29, 34]. Finally, smoking might exacerbate the development of abnormal neuromuscular processing and chronic pain due to vasoconstriction and psychological sensitivity [9, 35].

The fact that only approximately half of AS patients benefit from treatment with their first TNFi [1, 4, 36, 37] has fuelled the search for baseline predictors of treatment response in individual patients [6]. However, many previous observational and randomized studies have not included data on smoking status [5, 6, 38, 39]. We found that current smokers had significantly poorer TNFi treatment adherence and treatment effect than never smokers. This is in accordance with a recent Swiss cohort study of 698 patients with axSpA, of whom ~20% had non-radiographic axSpA, and in which current smokers had an OR of 0.54 (0.31 to 0.95) for achieving BASDAI50% reduction after one year's treatment compared with never smokers [16]. Other studies have found no such association. Among 422 Australian TNFi-treated AS patients, smoking had no effect on health-related quality of life [17]. The authors suggested that their inclusion of educational level in the multivariate analyses partly explained this because they found significant differences when educational level was omitted from the regression model [17]. In the current study, we had no data on educational level, and this may have influenced our results. An English cohort study based on data from the British Society for Rheumatology Biologics Register (BSRBR) did not find

Table 2 Impact of smoking on treatment adherence stratified by gender

		Overall		Men		Women	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Univariate analyses	Smoking status						
	Current	1.32 (1.14, 1.53)	<0.0001	1.41 (1.17, 1.69)	<0.0001	1.32 (1.04, 1.70)	0.03
	Previous	1.24 (1.02, 1.50)	0.03	1.35 (1.06, 1.71)	0.01	1.18 (0.83, 1.68)	0.4
	Never	1		1		1	
Multivariate analyses	Smoking status						
	Current	1.41 (1.21, 1.65)	<0.0001	1.49 (1.23, 1.82)	<0.0001	1.21 (0.93, 1.59)	0.15
	Previous	1.38 (1.12, 1.65)	0.003	1.39 (1.07, 1.80)	0.01	1.34 (0.93, 1.93)	0.12
	Never	1		1		1	
	Gender						
	Women	1.64 (1.41, 1.91)	<0.0001	—	—	—	—
	Men	1					
	Disease duration, years						
	0–1	1.45 (1.22, 1.73)	<0.0001	1.28 (1.04, 1.59)	0.02	1.97 (1.41, 2.74)	<0.0001
	2–7	1.34 (1.11, 1.63)	0.003	1.21 (0.96, 1.52)	0.11	1.77 (1.22, 2.57)	0.004
	⩾8	1		1		1	
	Age, years						
	⩽31	1.02 (0.82, 1.25)	0.9	0.91 (0.71, 1.19)	0.5	1.23 (0.86, 1.78)	0.3
	32–39	0.86 (0.70, 1.06)	0.17	0.77 (0.59, 1.00)	0.05	1.03 (0.72, 1.46)	0.9
	40–49	1.08 (0.89, 1.31)	0.4	1.05 (0.84, 1.32)	0.7	1.09 (0.77, 1.55)	0.6
	⩾50	1		1		1	
	TNFi start year						
	2000–06	0.70 (0.58, 0.86)	<0.0001	0.69 (0.54, 0.88)	0.003	0.79 (0.57, 1.11)	0.18
	2007–09	0.89 (0.74, 1.06)	0.2	0.93 (0.74, 1.17)	0.5	0.86 (0.64, 1.15)	0.3
	2010–13	1		1		1	

Univariate and multivariate Cox regression analyses (including *a priori* confounders). MTX use and TNFi drug type did not alter the HR of smoking by >10% and was not included in the multivariate analyses. HR: hazard ratio for withdrawal; TNFi: TNF-α inhibitor.

that smoking status among the baseline factors predicted BASDAI response in AS patients. However, with only 261 patients (94 current smokers) that study may have been insufficiently powered to answer this question [36]. Furthermore, the multivariate analyses included possible intermediate variables (CRP, BASDAI and BASFI) between smoking and outcome. This might have caused overadjustment bias. Any negative effect of smoking on TNFi treatment effects may be due to elevated inflammatory biologic parameters or increased matrix metalloproteinase levels, which are also predictive factors [40]. According to our study and the Swiss results [16], smoking status seems to be an important risk factor, and future studies should consider including such data.

In the current study, previous smokers had similar treatment duration and treatment effects to those of current smokers. Previous smokers who had stopped smoking ⩾6 years prior to TNFi start had similar treatment duration to the patients who had stopped smoking in recent years. This indicates a permanent negative impact of smoking. Contrasting results were found by Ciurea *et al.* [16] among PsA and RA patients, where previous smokers resemble never smokers—especially if smoking cessation happened many years ago [21, 22, 41]. The negative effects of previous smoking on outcome measures in the current study might partly be explained by the fact that previous smokers were older and had a longer disease duration than never smokers—although adjustment for these differences did not alter the association. Any potential differences in the effect of modification of smoking across rheumatic diseases remain unexplained. However, these diseases have different age and gender profiles, inflammatory and immune responses, and a uniform smoking effect is not necessarily to be expected [17]. Furthermore, previous studies in the general population have shown that smoking increases the prevalence of lower back pain and degenerative diseases of the back [42–44], which may contribute to the negative impact of ever smoking in AS.

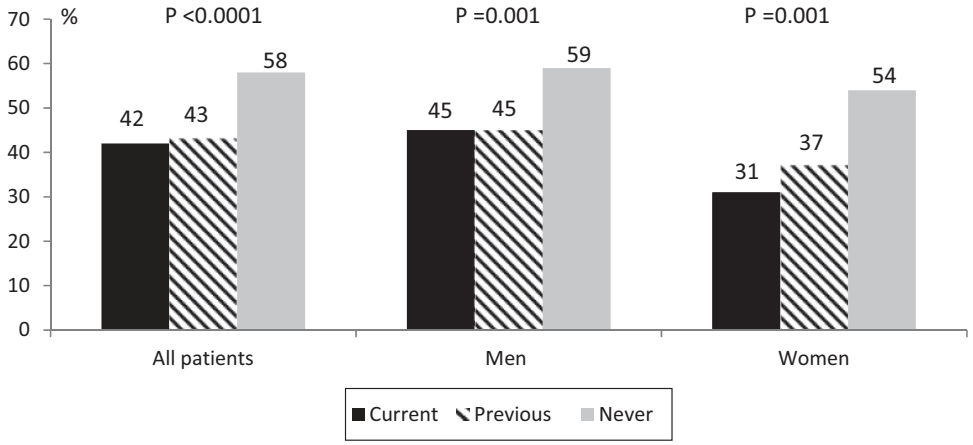
The strengths of this study are the high external validity for routine care, owing to the inclusion of an unselected, nationwide, large population of patients with AS with long follow-up time and known smoking status in 90% of cases. Base-line characteristics and drug adherence were largely the same in patients with missing and known smoking status, which contradicts substantial selection bias. Our study also has limitations. Smoking status was retrieved cross-sectionally at commencement of the first TNFi, although smoking status might later change [21]. An obvious misclassification occurs when previous smokers resume smoking during follow-up. We had no data on duration of smoking or pack-years to

Table 3 Impact of smoking on treatment adherence stratified by TNFi drug type

		Adalimumab		Etanercept		Infliximab	
Treatment adherence, Kaplan–Meier analyses							
		Median (95% CI)	**P**	**Median (95% CI)**	**P**	**Median (95% CI)**	**P**
Treatment adherence[a], years	Smoking status						
	Current	2.80 (2.01, 3.59)	0.02	2.29 (0.39, 4.20)	0.009	1.93 (1.19, 2.67)	0.07
	Never	5.73 (4.08, 7.38)		7.56 (4.03, 11.08)		3.50 (2.46, 4.53)	
Multivariate Cox regression analyses							
		HR (95% CI)	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Multivariate analyses	Smoking status						
	Current	1.33 (1.02, 1.74)	0.04	2.09 (1.38, 3.18)	<0.001	1.33 (1.05, 1.69)	0.02
	Previous	1.41 (1.02, 1.94)	0.04	2.16 (1.24, 3.77)	0.006	1.21 (0.85, 1.73)	0.3
	Never	1		1		1	
	Gender						
	Women	1.79 (1.41, 2.27)	<0.0001	1.92 (1.28, 2.89)	0.002	1.42 (1.12, 1.81)	0.004
	Men	1		1		1	
	Disease duration, years						
	0–1	1.51 (1.12, 2.02)	0.006	1.32 (0.85, 2.04)	0.2	1.42 (1.08, 1.88)	0.01
	2–7	1.43 (1.04, 1.96)	0.03	1.02 (0.60, 1.73)	0.9	1.43 (1.07, 1.91)	0.02
	⩾8	1		1		1	
	Age, years						
	⩽31	1.03 (0.73, 1.45)	0.9	1.05 (0.60, 1.85)	0.9	1.07 (0.76, 1.50)	0.7
	32–39	0.79 (0.56, 1.11)	0.2	1.15 (0.69, 1.94)	0.6	0.90 (0.65, 1.25)	0.5
	40–49	1.07 (0.78, 1.47)	0.7	0.92 (0.57, 1.48)	0.9	1.14 (0.85, 1.54)	0.4
	⩾50	1		1		1	
	TNFi start year						
	2000–06	0.62 (0.42, 0.90)	0.01	0.38 (0.23, 0.64)	<0.0001	0.67 (0.47, 0.95)	0.02
	2007–09	0.87 (0.67, 1.13)	0.3	0.66 (0.41, 1.06)	0.09	0.86 (0.61, 1.23)	0.4
	2010–13	1		1		1	

Log rank tests[a] and multivariate Cox regression analyses (including *a priori* confounders). MTX use did not alter the HR of smoking by >10% and was not included in the multivariate analyses. HR: hazard ratio for withdrawal; TNFi: TNF-α inhibitor

Fig. 2 BASDAI50%/20 mm-response rates after 6 months' treatment according to smoking status for all patients and stratified according to gender



P-values are response rates among current versus never smokers (Chi square).

TABLE 4 Impact of smoking on treatment response for all patients, stratified by gender and TNFi drug type

	Overall		Men		Women	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Smoking status						
Current	0.48 (0.35, 0.65)	<0.0001	0.55 (0.38, 0.80)	0.001	0.34 (0.19, 0.62)	<0.001
Previous	0.53 (0.35, 0.80)	0.002	0.60 (0.37, 0.97)	0.04	0.40 (0.18, 0.88)	0.02
Never	1		1		1	
	Adalimumab		Etanercept		Infliximab	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Smoking status						
Current	0.45 (0.27, 0.76)	0.002	0.24 (0.10, 0.61)	0.003	0.57 (0.34, 0.95)	0.03
Previous	0.58 (0.31, 1.10)	0.1	0.29 (0.10, 0.91)	0.03	0.58 (0.29, 1.14)	0.11
Never	1		1		1	

Multivariate logistic regression analyses including *a priori* confounders (odds ratios for confounders not shown in table). MTX use did not alter the HR of smoking by >10% and was not included in the analyses. OR: odds ratio; TNFi: TNF-α inhibitor.

illustrate any dose–response relationship [9, 15]. In Denmark, heavy smokers are more often men [45, 46]. One might assume that the stronger impact of smoking among male patients was associated with greater exposure to tobacco. Smoking may be linked to comorbid disease, depression, socioeconomic factors and lifestyle, which all potentially affect baseline disease activity and treatment outcomes. We had no data with which to explore these issues further. In DANBIO, the clinical diagnosis for individual patients was registered according to the expert opinion of the treating physician. Currently, data regarding HLAB27 status, radiographic data and peripheral joint disease are not uniformly available in DANBIO. In conclusion, this study of AS patients treated with TNFi in clinical practice showed that current and previous smokers had significantly poorer patient-reported outcomes at baseline, shorter treatment adherence and poorer treatment response compared with never smokers.

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