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ORIGINAL RESEARCH

Evaluation of long-term TNFi effectiveness after a first switch in early axial spondyloarthritis considering time-varying prescription bias: an inverse-probability weighting analysis of the DESIR cohort

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ABSTRACT

Objective To evaluate long-term effectiveness of tumour necrosis factor inhibitor (TNFi) after a first switch, and their associated factors in an early axial spondyloarthritis (axSpA) population, considering time-varying prescription bias.

Methods Observational prospective cohort (DEvenir des Spondylarthropathies Indifférenciées Récentes) with 5 years of follow-up, including 708 TNFi-naïve patients with early axSpA. Long-term effectiveness of TNFi after a first switch (ASAS40 response after at least 2 visits under treatment) were estimated using marginal structural models (implementing inverse-probability weighting and iterative propensity scores). Factors associated with the outcome were explored by multivariate Cox regression models.

Results The hazard to present an ASAS40 response after a first TNFi switch was increased (HR=2.4 (95% CI 1.9 to 3.0)); this response ratio was slightly lower compared with the response in TNFi naïve patients after a first TNFi (HR=3.3 (95% CI 2.9 to 3.8)). HLA-B27 positive was the only factor independently associated with ASAS40 response after a first TNFi switch.

Conclusion After application of innovative methods to overcome time-varying prescription bias, the magnitude of the TNFi response after a first switch was found to be numerically lower but clinically relevant from the response in TNFi-naïve patients.

Key messages

What is already known about this subject?

► Some divergent data have been reported on the effectiveness of a second-line tumour necrosis factor inhibitor (TNFi): while some observational studies suggest that effectiveness of a second-line TNFi after one switch can be comparable to the first one in patients with ankylosing spondylitis, some others report lower retention rates for the second compared with the first one.

What does this study add?

► We evaluated the efficacy of a first TNFi switch in an observational cohort in early axial spondyloarthritis while applying the most innovative statistical technique to avoid prescription bias: the inverse-probability weighting method, which is a novelty in the field of rheumatology and better reflects real-life prescriptions.

How might this impact on clinical practice or further developments?

► With this approach, we found a poorer TNFi effectiveness after a first switch in real-life conditions (2.4-fold probability to respond to a TNFi after a first switch, vs a threefold probability in TNFi-naïve patients), but still clinically relevant.

The major advance in the treatment of axial spondyloarthritis (axSpA) patients is the arrival of tumour necrosis factor α inhibitors (TNFi) in the early 2000s. Evidence around their efficacy is appalling, with multiple randomised clinical trials (RCT) both in radiographic and non-radiographic forms[1–11] reporting results in this direction.

However, even if RCT are considered the gold-standard for the evaluation of efficacy, they do not always yield relevant information about the effects in a particular target population (known as 'external validity').[12] This concern with regard to the external validity of trials has led to gain interest in 'Real World Evidence' (ie, observational data) as these data might provide more appropriate

evidence on treatment effectiveness in settings in which they may be typically applied. This is particularly important when evaluating situations such as a TNFi switch (ie, prescribing a second TNFi after failure of a first TNFi). TNFi discontinuation rates vary across trials, but have been reported to go as high as 60% in 2 years.[13] Some divergent data have been reported on the effectiveness of a second-line TNFi: while some observational studies suggest that effectiveness of a second-line TNFi after one switch can be comparable to the first one in patients with ankylosing spondylitis,[14 15] some other report lower retention rates for the second compared with the first one.[16]

Nevertheless, the evaluation of treatment effectiveness in observational data is faced to several challenges, mostly the prescription bias which is the association between the exposure and the prognostic patient characteristics. Indeed, in observational studies, the allocation of treatment is not random and the indication for treatment may be related to the risk of future health outcomes.[17] Patients who receive a given treatment are likely to be different from those who receive another treatment or remain untreated, given physician prescriptions are likely related to patient characteristics (eg, old patients with comorbidities are more likely to receive less 'aggressive' treatments). Therefore, one must account for systematic differences in characteristics between treated and untreated subjects when estimating the effect of treatment on outcomes, possibly confounding the estimation. Propensity score (PS) analysis has been proposed to adjust for bias by indication, and classically PS has been used to match the two groups of treatment at baseline (eg, at the start of a particular treatment). However, the analysis of effectiveness in longitudinal data raises another challenge, as indications may change over time, either in general (eg, when other classes of drug become available) or in individual patients (eg, because signs/symptom of the patients change over time). The inverse probability of treatment weighting (IPTW) method based on the PS is a statistical method that allows handling repeated treatment decisions and avoiding prescription bias over time.

In the specific case of TNFi in axSpA, short-term effectiveness of a first TNFi (ie, their efficacy in observational trials) has been reported,[18] but in these analyses only baseline matching by the PS was performed and the potential time-changing nature of TNFi indication was not considered. Furthermore, to date no study has aimed to evaluate the long-term effectiveness after a first TNFi switch considering time-varying prescription bias over follow-up.

All these previous remarks prompted us to investigate the long-term effectiveness of TNFi after a first switch (ie, the second TNFi) in a multicentre French observational inception cohort of patients with early axSpA, while adjusting for prescription bias over time.

PATIENTS AND METHODS

Patients

A total of 708 patients with early inflammatory back pain (IBP) were included in the DESIR (DEvenir des Spondylarthropathies Indifférenciées Récentes) cohort between 2007 and 2010.[19] The analyses in the present study include the first 5 years of follow-up (Clinical Trial.gov identifier: NCT01648907).

Patients between the ages of 18 and 50 years with IBP involving the thoracic spine, lumbar spine or buttocks area for 3 months but <3 years and with symptoms highly suggestive of axSpA according to their rheumatologist (score >5 on a Numerical Rating Scale of 0–10, where 0=not suggestive of axSpA and 10=very suggestive of axSpA) were included in the study. Patients were required to fulfil the Calin *et al*[20] or the Berlin[21] criteria for IBP. Patients with a definitive alternative diagnosis different from axSpA, any condition that could affect the validity of the informed consent and/or prevent the patient from achieving optimal compliance (ie, alcoholism, psychiatric disorder), or with previous exposure to TNFi were excluded. All 708 patients from the DESIR cohort were included in our analysis. The DESIR dataset used for this analysis was locked on June 2017.

Definition of visits

Study visits were scheduled every 6 months in the first 2 years of follow-up then yearly up to 5 years. Patients could receive any treatment at any time during follow-up at the discretion of their treating rheumatologists. Since patients could start a TNFi at any moment during the follow-up (and not specifically at the time of the DESIR study visit) a 'pre-TNFi visit' and a 'long-term effectiveness visit' had to be defined for each patient initiating a TNFi: 'pre-TNFi visit' was defined as the visit occurring just before the initiation of the TNFi or the visit occurring within 7 days after such initiation; the 'long-term effectiveness visit' was defined as the second consecutive visit under treatment or 10 months under treatment.

Data collected

All variables collected at each DESIR cohort visit have been described elsewhere.[19] Patients' characteristics (age, sex, sociodemographic features, smoking status, employment), SpA clinical features (date of disease onset, peripheral involvement, enthesitis), disease activity (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[22 23]Ankylosing Spondylitis Disease Activity Score and C reactive protein (CRP) (mg/L)) and severity (Bath Ankylosing Spondylitis Functional Index (BASFI)[24]), and local reading imaging (radiographic sacroiliitis, MRI sacroiliitis) were collected at each DESIR visit according to the study protocol (detailed protocol and collected variables information are available online at wwwlacohortedesirfr/desir-in-english).

Interventions

TNFi initiation (time, indication and molecule) was at the discretion of the treating rheumatologist. Patients initiating a biological other than TNFi were excluded from this analysis (only three patients).

In order to compare the long-term effectiveness of a second TNFi after a first switch, we also estimated the long-term effectiveness of a first TNFi in this TNF-naïve cohort of early axSpA patients.

Two treatment groups were considered.

- To estimate the long-term effectiveness of the first TNFi, all patients receiving at least one TNFi over the 5 years of follow-up (ie, 'first TNFi' group) were compared with all patients receiving any other treatment, except for biologicals (ie, 'usual care' group).
- To estimate the long-term effectiveness of the second TNFi, all patients receiving at least a second TNFi over the 5 years of follow-up (ie, 'second TNFi' group) were compared with patients from the 'first TNFi' group.

Outcomes

Long-term effectiveness

was defined as the occurrence of an ASAS40 response (defined as an improvement of at least 40% and an absolute improvement of at least two units (on a scale of 0–10) compared with baseline, in three or more of the four domains (BASFI, patient's assessment of pain, patient's assessment of disease activity and mean score from question 5 and 6 on the BASDAI), and with no worsening at all in the remaining domains)[25] after at least 10 months under treatment in the TNFi group. In the usual care group, ASAS40 response was estimated between two consecutive visits.

Patients excluded

Patients lost to follow-up or patients who stopped TNFi before 10 months of exposure (or two consecutive visits) were excluded from the analyses. Indeed, in the DESIR cohort, the reason why the treatment stopped was not collected at this time of the follow-up.

Statistical analysis

Summary statistics, namely median (IQR) and percentages, are reported.

Long-term effectiveness of a first TNFi switch

In order to reduce prescription bias when estimating long-term treatment effect in a time-varying exposure to TNFi, marginal structural models (MSM) with IPTWs were used, in order to include weighted observations according to the (time-varying) probability of the patients to receive a given treatment over time. This approach examines the differences in treatment histories to measure the marginal impact of being treated with TNFi over the course of the observed data. Weights were derived from PS, which is the probability to receive a particular treatment (here, the second TNFi after a first TNFi), conditioned on the patient characteristics (eg, age or comorbidities) at the time of treatment decision. In the absence of randomisation, it allows to overcome imbalances in treated and untreated patients.[26] In this particular case of time-varying exposure to TNFi (ie, a TNFi could be prescribed at any time over follow-up), imbalances between treated/untreated patients could change also over time: thus, the MSM controls for time-dependent confounders and using time-dependent weights, produce a pseudo-population with balance in both time-invariant and time-varying covariates allowing for causal treatment comparisons using standard regression models.[27] For each TNFi switch, a PS was thus estimated at each visit (the variables introduced in the PS were selected on both their clinical relevance and their association with the outcome). Second, inverse probability weights (IPWs) were derived from the PS at each visit.[28] PS models (detailed in online supplemental table 1) were selected on the ability to reduce imbalances in covariates after weighting, as measured on standardised mean differences (SMD) below 0.1 as much as possible, and c-index (AUC, area under the curve) closest to 0.5.[28] All the SMD before and after weighting, are summarised in online supplemental figure 1 for the second TNFi. Finally, a PS-weighted Cox regression (ie, a structural marginal model) was used to estimate the probability to present an ASAS40 response at the 'long-term efficacy visit' after a second TNFi prescription.

We also evaluated the long-term effectiveness of a first TNFi in DESIR, in order to be able to put in context the effectiveness results of a second TNFi with the exact same methodology. (All diagnostics of the standardised differences before and after weighting, using the PSs are summarised in online supplemental figure 2 for the first TNFi.) Identically, a PS-weighted Cox regression (ie, a structural marginal model) was used to estimate the probability to present an ASAS40 response at the 'long-term efficacy visit' after a first TNFi prescription.

In order to infer causality from observational data, assumptions are required. The exchangeability assumption (ie, 'no unmeasured confounders') was checked by constructing different models of PSs, including many potential confounders selected on both clinical relevance and prognostic value on the sample, and retained that score with the best balance diagnostics as described above. In the context of patient exposed to TNFi, the consistency hypothesis, that requires that the outcome observed for each individual is precisely the causal outcome under their observed treatment history, was likely validated because treatment exposure could be defined unambiguously.[29] The positivity assumption that there are both exposed and unexposed individuals at all levels of confounding factors, was likely to be valid, given there were no evident situations where the treatment assignment was deterministic, and the large sample size likely limited the occurrence of random zeros in some covariate levels. Nevertheless, we checked that the mean of weights was close to 1, that further suggested no evidence of violation of the model assumptions.

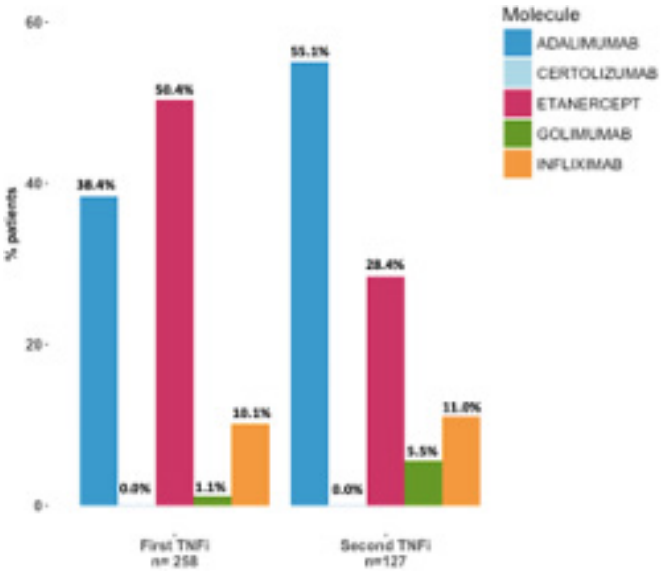

Figure 1 TNFi distribution in TNFi-naïve (first TNFi) and TNFi-switched (second TNFi) patients. TNFi, tumour necrosis factor inhibitor.

Factors associated with first and second TNFi effectiveness, were explored by univariate and then multivariate Cox regression. To be included in the multivariable analysis, variables needed to be associated (p<0.2) with drug survival in the univariate analysis.

Statistical analysis was performed on R V.3.4.3 (https://www.R-project.org/).

RESULTS

Long-term effectiveness TNFi after a first switch

Of the 708 patients included in the analysis, 258 (36.4%) TNF-naïve patients initiated a TNFi during the first 5 years of follow-up. Among the 258 patients who started, 127 (49.2%) underwent a first switch: among them 70 (55.1%) received adalimumab, 36 (28.4%) etanercept, 14 (11.0%) infliximab and 7 (5.5%) golimumab, respectively (figure 1). Table 1 summarises the baseline characteristics of the 127 patients who underwent a first switch. Among the 127 patients, 78 patients (61.4%) were exposed to the switched TNFi for at least 10 months, and

Table 1 Baseline characteristics of the 258 patients initiating the first TNFi, the 127 patients switching for a second TNFi and the rest of the cohort

Baseline characteristics*	Patients receiving a TNFi over the 5 years of follow-up N=258	Patients switching to a second TNFi over the 5 years of follow-up N=127	Patients receiving usual care† N=450	P value‡
Age (years)	34.0 (9.0)	35.3 (8.7)	34.6 (8.4)	0.53
Sex (male)	113 (43.8)	40 (31.5)	213 (47.3)	0.35
Symptoms duration (years)	1.5 (0.9)	1.6 (0.9)	1.5 (0.9)	0.53
Employment (blue collar)	42/256 (16.4)	23/126 (18.3)	63/445 (14.3)	0.42
Education (university)	**133 (51.6)**	64 (50.4)	**284/445 (63.8)**	**0.001**
HLA-B27 positive	147 (57.0)	62 (48.8)	263/448 (58.7)	0.65
MRI sacroiliitis positive	**105/253 (41.5)**	39/125 (31.2)	**130/438 (29.7)**	**0.002**
Radiographic sacroiliitis positive	**57/254 (22.4)**	17 (13.4)	**55/439 (12.5)**	**<0.001**
History of good NSAID response	221/257 (86.0)	104/126 (82.5)	376/444 (84.7)	0.64
History of arthritis	**89/256 (34.8)**	37/125 (29.6)	**102/446 (22.9)**	**<0.001**
History of dactylitis	39/257 (15.2)	16/126 (11.9)	58/447 (13.0)	0.41
CRP (mg/L)	**12.5** (19.1)	10.5 (19.8)	**5.3** (7.8)	**<0.001**
ASDAS-CRP	**3.1** (0.9)	3.2 (0.8)	**2.4** (0.9)	**<0.001**
BASDAI (range 0–10)	**5.3** (1.7)	5.9 (1.5)	**4.0** (2.0)	**<0.001**
BASFI (range 0–10)	**4.0** (2.2)	4.6 (2.1)	**2.5** (2.2)	**<0.001**
Centre in which TNFi prescription rate was >30% over follow-up	**201 (77.9)**	97 (76.4)	**237 (52.7)**	**<0.001**
Presence of at least one objective sign of inflammation****	**159/252 (63.1)**	60/125 (48.0)	**192/426 (45.1)**	**<0.001**

***Comparing the first TNFi to the rest of the cohort.
*Values are presented as mean (SD) and n (%) for continuous and categorical variables, respectively.
†Usual care=any (non-biological) treatment other than TNFi.
‡Objective sign of inflammation is the presence of at least a systemic increased CRP (≥6 mg/L) or local inflammation (MRI sacroiliitis) or structural damage of the sacroiliac joint.
ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score using CRP; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C reactive protein; NSAID, non-steroidal anti-inflammatory drugs; TNFi, tumour necrosis factor inhibitor.

Table 2 Factors associated with continuation of the switched TNFi

Baseline characteristics*	Patients continuing the switched TNFi: Yes (n=39)	No (n=85)	Univariate HR (95% CI)	Multivariate HR (95% CI)	P value
Age (years) (≥45 years old)	6 (15.4)	13 (15.3)	1.1 (0.6 to 1.9)	_	_
Sex (male)	14 (35.9)	26 (30.6)	1.3 (0.8 to 1.9)	_	
Initiation of treatment ≤18 months	6 (15.4)	48 (56.5)	0.7 (0.5 to 1.1)	0.99 (0.6 to 1.6)	0.95
Employment (blue collar)	10/38 (26.3)	13 (15.3)	1.4 (0.8 to 2.6)	_	_
Education (university)	20 (51.3)	41 (48.2)	1.3 (0.8 to 2.0)	_	_
HLA-B27 positive	**23** (59.0)	**38** (44.7)	**1.6 (1.1 to 2.5)**	**1.8 (1.1 to 2.8)**	**0.01**
MRI sacroiliitis positive	17 (43.6)	22/83 (26.5)	1.3 (0.8 to 2.0)	_	_
Radiographic sacroiliitis positive	6 (15.4)	11 (12.9)	1.1 (0.6 to 2.1)	_	_
History of good NSAID response	32 (82.1)	70/84 (83.3)	0.9 (0.5 to 1.6)	_	_
NSAID score week	50.6 (46.1)	65.1 (55.7)	1.1 (1.0 to 1.1)	1.1 (1.0 to 1.1)	0.06
History of arthritis	9/38 (23.7)	26/84 (31.0)	1.2 (0.7 to 1.9)	_	_
History of dactylitis	1 (2.6)	13/84 (15.5)	0.7 (0.4 to 1.3)	_	_
History of enthesitis	29 (74.4)	63 (74.1)	1.0 (0.6 to 1.6)	_	_
CRP (≥6 mg/L)	14 (35.9)	24/83 (28.9)	1.2 (0.7 to 1.9)	_	_
ASDAS-CRP (per point)	3.1 (0.7)	3.3 (0.9)	0.9 (0.7 to 1.2)	_	_
BASDAI (range 0–10)	5.6 (1.6)	6.0 (1.4)	0.9 (0.8 to 1.1)	_	_
Presence of at least one objective sign of inflammation or structural damage	18/37 (48.6)	27/83 (32.5)	1.2 (0.7 to 1.9)	_	_
BASFI (range 0–10)	4.2 (2.2)	4.8 (2.1)	1.0 (0.9 to 1.1)	_	_
Centre in which TNFi inclusion rate was over 20% over follow-up	32 (82.1)	67 (78.8)	1.0 (0.6 to 1.7)	_	_
Centre in which TNFi prescription rate was over 30% over follow-up	**23** (59.0)	**72** (84.7)	**0.5 (0.3 to 0.9)**	**0.4 (0.2 to 0.8)**	**0.01**

*Values are presented as mean (SD) and n (%) for continuous and categorical variables, respectively.
ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score using CRP; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C reactive protein; NSAID, non-steroidal anti-inflammatory drugs; TNFi, tumour necrosis factor inhibitor.

their ASAS40 response rate was 19.2%. The hazard of an ASAS40 response after a first TNFi switch was increased by twofold (HR (marginal structural Cox model)=2.4 (1.9 to 3.0), p<0.0001). The only factor independently associated with a long-term effectiveness after a first TNFi switch was HLA-B27 positive (HR=1.8 (95% CI 1.1 to 2.8), p=0.01) (table 2).

Long-term effectiveness of TNFi prescription in naïve patients

Among the 258 TNFi-naïve patients initiating a TNFi, 130 (50.4%) received Etanercept, 99 (38.4%) adalimumab, 26 (10.1%) infliximab and 3 (1.1%) golimumab, respectively (figure 1). Among them, 163 patients (63.2%) were exposed to the TNFi for at least 10 months, and the ASAS40 response rates were 50/163 (30.7%) versus 58/450 (12.9%) in the treatment and usual cares groups), respectively. The hazard of an ASAS40 response was threefold increased in the TNFi group (HR (marginal structural Cox model)=3.3 (2.9 to 3.8), p<0.001).

Factors independently associated with first TNFi effectiveness were male gender (HR=1.5 (95% CI 1.1 to 2.1)), HLA-B27 positive (HR=1.4 (95% CI 1.1 to 2.0)), and the presence of at least one objective sign of inflammation (systemic (increased CRP) or local (MRI sacroiliitis) or structural damage of the sacroiliac joints (SIJ)) (HR=1.7 (95% CI 1.2 to 2.4)) (table 3).

TNFi drug-survival curves for naïve and switched patients are represented in figure 2.

DISCUSSION

In this population of recent axSpA, we evaluated the hazard of treatment response after a first TNFi switch, by applying innovating methods to try to overcome time-varying prescription bias (eg, IPW and MSM). In our study, there was a 2.4 times greater hazard to respond to a TNFi after a switch, compared with a three times greater hazard in TNFi-naïve patients; the probability of response was indeed lower for a second TNFi, but the difference compared with a first TNFi was comparable to long-term ASAS40 response rates observed in non-radiographic

Table 3 Factors associated with TNFi continuation in naïve patients

Baseline characteristics*	Patients continuing the first TNFi				
	Yes (n=88)	No (n=154)	Univariate HR (95% CI)	Multivariate HR (95% CI)	P value
Age (years) (≥45 years old)	14 (15.9)	22 (14.3)	1.1 (0.7 to 1.7)	_	_
Sex (male)	**52** (59.1)	**52** (33.8)	**2.0 (1.4 to 2.7)**	**1.5 (1.1 to 2.1)**	**0.04**
Symptoms duration (years)	1.5 (0.9)	1.6 (0.9)	0.9 (0.8 to 1.1)	_	_
Employment (blue collar)	13/87 (14.9)	25/153	1.1 (0.7 to 1.6)	_	_
Education (university)	45 (51.1)	81 (52.6)	1.1 (0.7 to 1.4)	_	_
HLA-B27 positive	**57** (64.8)	**79** (51.3)	**1.6 (1.1 to 2.1)**	**1.4 (1.1 to 2.0)**	**0.03**
MRI sacroiliitis positive	46/85 (54.1)	51/152 (86.2)	1.8 (1.3 to 2.6)	_	_
Radiographic sacroiliitis positive	27/85 (31.8)	26/153 (17.0)	1.9 (1.2 to 2.9)	_	_
History of good NSAID response	79 (89.8)	128/153 (83.7)	1.1 (0.7 to 1.7)	_	_
History of arthritis	31 (35.2)	50/152 (32.9)	1.2 (0.8 to 1.6)	_	_
History of dactylitis	12 (13.6)	23/153 (15.0)	1.1 (0.7 to 1.7)	_	_
History of enthesitis	54 (61.4)	115 (74.7)	1.5 (1.0 to 2.1)	1.4 (0.9 to 2.0)	0.11
CRP (mg/L)	13.1 (14.4)	10.9 (19.5)	1.0 (1.0 to 1.1)	_	_
ASDAS-CRP (per point)	**2.9** (0.9)	**3.2** (0.8)	**0.8 (0.7 to 1.0)**	**0.8 (0.6 to 0.9)**	**0.02**
BASDAI (range 0–10)	4.5 (1.8)	5.8 (1.5)	0.8 (0.7 to 0.9)	_	_
Presence of at least one objective sign of inflammation or structural damage	**53/85** (62.4)	**61/149** (40.9)	**2.0 (1.4 to 2.8)**	**1.7 (1.2 to 2.4)**	**0.004**
BASFI (range 0–10)	3.1 (2.1)	4.4 (2.1)	0.9 (0.8 to 0.9)	_	_
Centre in which TNFi inclusion rate was over 20% over follow-up	59 (67.0)	126 (81.8)	1.6 (1.1 to 2.4)	1.3 (0.8 to 1.9)	0.36
Centre in which TNFi prescription rate was over 30% over follow-up	71 (80.7)	117 (76.0)	1.2 (0.8 to 1.6)	_	_

*Values are presented as mean (SD) and n (%) for continuous and categorical variables, respectively.
ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score using CRP; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C reactive protein; NSAID, non-steroidal anti-inflammatory drugs; TNFi, tumour necrosis factor inhibitor.

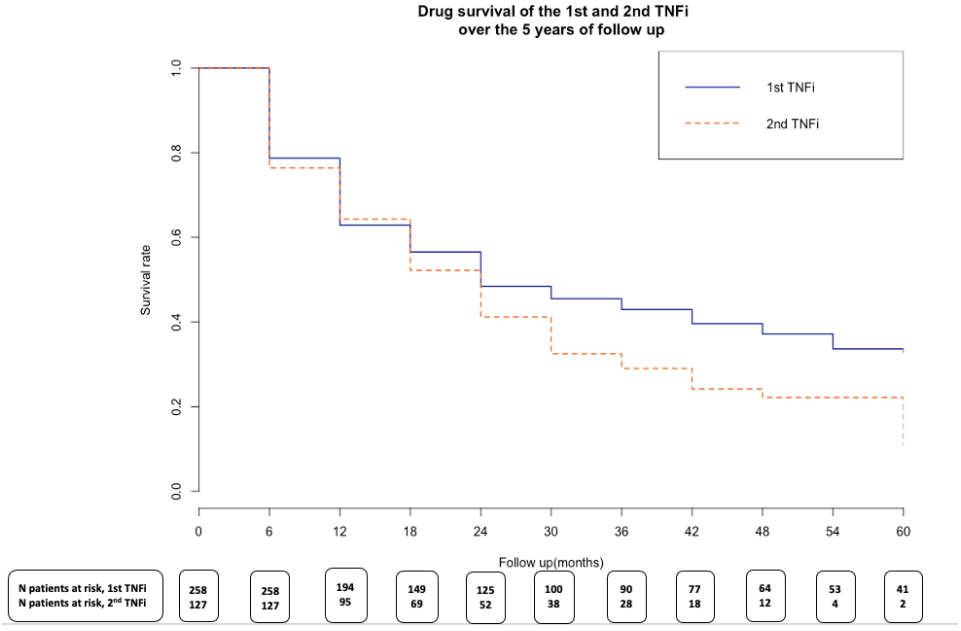

Figure 2 TNFi drug survival for TNFi-naïve (first TNFi) and switched (second TNFi) patients. TNFi, tumour necrosis factor inhibitor.

axSpA RCT[30] but also to data from other observational cohorts.[31 32]

Furthermore, our analysis suggests that male patients, HLAB27 carriers and patients presenting with at least one objective sign of local (MRI SIJ) or systemic inflammation (CRP) or structural damage of the SIJ are more likely to respond to a first TNFi, while only HLAB27+ was independently associated with greater response after a switch. Our results are in agreement with the literature, where many factors have been reported to be associated with treatment response to TNFi in axSpA (eg, younger age, shorter disease duration, elevated CRP, BASDAI, BASFI, HLA-B27 positivity and objective signs of inflammation).[33–37](p1)

This study has some limitations but also some strengths. First, the DESIR cohort included patients presenting with chronic IBP and a confidence in an axSpA diagnosis >5/10 by a rheumatologist. Although rheumatologists were asked at the end of each visit whether another diagnosis was more likely so that patients with an inappropriate diagnosis could be excluded from the study, it is not impossible that the cohort included patients with conditions other than axSpA (eg, IBP linked to degenerative disc disease). However, the vast majority of patients in the study (95.9%) fulfilled at least one set of criteria for SpA.[19]

Second, as previously mentioned, evaluating treatment effect in observational trials is methodologically challenging, namely because of indication bias, with a time-varying probability to receive such treatment. In our analysis, we have applied the most recent methods (eg, IPW and MSM) to try to overcome such problem (ie, time-varying prescription bias occurring over time) bringing our study closer to a pragmatic 'pseudorandomised' trial and providing valuable data on real-life treatment effects. Underlying assumptions are obviously required to ensure the validity of MSM estimates, and notably, one cannot exclude that some confounders have been unmeasured, resulting in some residual confounding bias. Nevertheless, exchangeability appears to have been reached owing to the balance diagnostics after weighting. Moreover, there were no evidence of violation of the positivity assumption or of any misspecification of the models.

Third, extra-articular manifestations are very important covariates and could be the reason for TNFi prescription or switch in clinical practice. As recommended, covariates introduced in the PS were selected on both clinical relevance and association on the sample with the outcome (ASAS40 response) at the 0.20 level. None of the extra-articular manifestations were associated with the ASAS40 response with 0.20 level. But, based on their clinical relevance, we tried to include those covariates in the PSs. However, the PS retained were selected on their ability to reduce imbalances in covariates after weighting, and those with extra-articular manifestations were not included.

Furthermore, this analysis is, to the authors' best knowledge, the largest prospective observational cohort of patients with early axSpA analysing long-term effectiveness of TNFi after a first switch of TNFi in a real-life clinical setting.

Our study suggests a clinically relevant effectiveness of TNFi after a first switch compared with a TNFi response in naïve patients. Further analyses evaluating whether the effectiveness of a switch to a second TNFi is comparable to a switch to another biological in a real-life setting are needed.

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REFERENCES

1 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;36:801–8.
2 Haibel H, Rudwaleit M, Listing J, *et al*. Efficacy of adalimumab in the treatment of axial spondylarthritis 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;58:1981–91.
3 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;72:815–22.
4 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;52:582–91.
5 Braun J, Brandt J, Listing J, *et al*. Long-Term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month, randomized, placebo-controlled trial. *Arthritis Rheum* 2003;48:2224–33.
6 Calin A, Dijkmans BAC, Emery P, *et al*. Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. *Ann Rheum Dis* 2004;63:1594–600.
7 Davis JC, van der Heijde DM, Braun J, *et al*. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. *Ann Rheum Dis* 2005;64:1557–62.
8 Dougados M, Heijde D, Sieper J, *et al*. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early Nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol* 2014;66:2091–102.
9 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.
10 Sieper J, Landewé R, Rudwaleit M, *et al*. Effect of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis: results from a phase III randomized trial. *Arthritis Rheumatol* 2015;67:668–77.
11 Inman RD, Davis JC, 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;58:3402–12.
12 Stuart EA, Bradshaw CP, Leaf PJ. Assessing the generalizability of randomized trial results to target populations. *Prev Sci* 2015;16:475–85.
13 Manica SR, Sepriano A, Pimentel-Santos F, *et al*. Effectiveness of switching between TNF inhibitors in patients with axial spondyloarthritis: is the reason to switch relevant? *Arthritis Res Ther* 2020;22:195.
14 Lie E, van der Heijde D, Uhlig T, *et al*. Effectiveness of switching between TNF inhibitors in ankylosing spondylitis: data from the NOR-DMARD register. *Ann Rheum Dis* 2011;70:157–63.
15 Moltó A, Etcheto A, Gossec L. THU0356 The rank of administration and not the molecule has an impact on the anti tnf treatment response in axial spa. *Ann Rheum Dis* 2017;76:339.
16 Deodhar A, Yu D. Switching tumor necrosis factor inhibitors in the treatment of axial spondyloarthritis. *Semin Arthritis Rheum* 2017;47:343–50.
17 Signorello LB, McLaughlin JK, Lipworth L, *et al*. Confounding by indication in epidemiologic studies of commonly used analgesics. *Am J Ther* 2002;9:199–205.
18 Moltó A, Paternotte S, Claudepierre P, *et al*. Effectiveness of tumor necrosis factor α blockers in early axial spondyloarthritis: data from the DESIR cohort. *Arthritis Rheumatol* 2014;66:1734–44.
19 Dougados M, Etcheto A, Molto A, *et al*. Clinical presentation of patients suffering from recent onset chronic inflammatory back pain suggestive of spondyloarthritis: the DESIR cohort. *Jt Bone Spine* 2015;82:345–51.
20 Calin A, Porta J, Fries JF, *et al*. Clinical history as a screening test for ankylosing spondylitis. *JAMA* 1977;237:2613–4.
21 Rudwaleit M, Metter A, Listing J, *et al*. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis Rheum* 2006;54:569–78.
22 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;21:2286–91.
23 Lukas C, Landewé R, Sieper J, *et al*. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009;68:18–24.
24 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;21:2281–5.
25 Brandt J, Listing J, Sieper J, *et al*. Development and preselection of criteria for short term improvement after anti-TNF alpha treatment in ankylosing spondylitis. *Ann Rheum Dis* 2004;63:1438–44.
26 Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 1997;127:757–63.
27 Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008;168:656–64.
28 Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015;34:3661–79.
29 Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008;168:656–64.
30 Anon A. Network meta-analysis of long-term efficacy (ASAS40) of biologic disease-modifying anti-rheumatic drugs (bDMARDs) in bDMARD-Naïve patients with non-radiographic axial spondyloarthritis. ACR meeting Abstracts. Available: https://acrabstracts.org/abstract/network-meta-analysis-of-long-term-efficacy-asas40-of-biologic-disease-modifying-anti-rheumatic-drugs-bdmards-in-bdmard-naive-patients-with-non-radiographic-axial-spondyloarthritis/ [Accessed 14 June 2021].
31 Ciurea A, Weber U, Stekhoven D, *et al*. Treatment with tumor necrosis factor inhibitors in axial spondyloarthritis: comparison between private rheumatology practices and academic centers in a large observational cohort. *J Rheumatol* 2015;42:101–5.
32 Corbett M, Soares M, Jhuti G, *et al*. Tumour necrosis factor-α inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation. *Health Technol Assess* 2016;20:1–334.
33 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.
34 Lord PAC, Farragher TM, Lunt M, *et al*. Predictors of response to anti-TNF therapy in ankylosing spondylitis: results from the British Society for rheumatology biologics register. *Rheumatology* 2010;49:563–70.
35 Maksymowych WP, Dougados M, van der Heijde D, *et al*. Clinical and MRI responses to etanercept in early non-radiographic axial spondyloarthritis: 48-week results from the EMBARK study. *Ann Rheum Dis* 2016;75:1328–35.
36 Vastesaeger N, van der Heijde D, Inman RD, *et al*. Predicting the outcome of ankylosing spondylitis therapy. *Ann Rheum Dis* 2011;70:973–81.
37 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;72:815–22.