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Original article

# Adherence to recommendations for the use of anti–tumour necrosis factor and its impact over 5 years of follow-up in axial spondyloarthritis

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## Abstract

**Objectives.** To describe adherence to recommendations for TNFα blocker (TNFb) initiation and continuation in early axial Spondyloarthropathy (axSpA); and to evaluate the impact of adherence to these recommendations over 5 years of follow-up in the DEvenir des Spondyloarthrites Indifférenciées Récentes (DESIR) cohort.

**Methods.** The first 5 years of follow-up of the DESIR early axSpA cohort were analysed. We evaluated adherence to Assessment of SpondyloArthritis International Society (ASAS) 2003/2006, 2016 and European Medicines Agency recommendations in axSpA patients for: TNFb initiation (patients were adherent if they either commenced TNFb therapy when they met the conditions for initiation or if they did not commence TNFb therapy when conditions were not met) and; TNFb continuation (either when they continued TNFb therapy when conditions to continue were met or when they discontinued when conditions were not met). The impact of adherence to these recommendations on functional disability, quality of life and sick-leave days over 5 years was explored.

**Results.** A total of 708 patients were analysed: 440 (62.15%), 389 (54.94%) and 335 (47.32%) were considered adherent to ASAS 2003/2006, 2016 and European Medicines Agency recommendations for TNFb initiation, respectively. Adherence to 2003/2006 and 2016 recommendations for TNFb continuation was observed in 47.37 and 49.39% of patients, respectively. According to over 5 years of follow-up, better outcomes (lower BASFI, higher SF-36 and fewer days of sick leave) were found in patients adhering to recommendations for TNFb commencement and continuation.

**Conclusion.** Less than 50% of patients were treated in agreement with recommendations for TNFb initiation and continuation. Nevertheless, adherence to such recommendations leads to better functional outcomes and fewer days of sick leave, according to long-term follow-up.

**Key words:** adherence, recommendations, TNF blockers, spondyloarthritis

CLINICAL SCIENCE

**Rheumatology key messages**

- Recommendations for the use of anti-tumour necrosis factor in axial SpA are well defined.
- Less than 50% of patients adhered to recommendations for use of TNFα blockers in axial SpA.
- Adherence to recommendations for TNFα blockers use leads to better long-term outcomes in axial SpA.

## Introduction

Spondyloarthropathy (SpA) is a chronic inflammatory disease that can present with different phenotypes, namely with axial SpA (axSpA) [1] or peripheral manifestations (peripheral SpA) [2]. In addition, the presence or absence of structural damage of the sacroiliac joints on X-rays (i.e. radiographic sacroiliitis) allows the classification of a patient into one of two main groups: patients with

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radiographic sacroiliitis (i.e. radiographic axSpA, r-axSpA) or without radiographic sacroiliitis (non-radiographic axSpA, nr-axSpA) [1].

NSAIDs are the cornerstone in the treatment. Nevertheless, the major recent advance in SpA treatment has been the use of TNFα blockers (TNFbs) [1, 3], which have proven to quickly reduce axial inflammatory symptoms and signs in axSpA patients in several randomized clinical trials [4–14].

According to both the first Assessment of SpondyloArthritis International Society (ASAS) recommendations for TNFb use in radiographic axSpA (r-axSpA) published in 2003 and the 2006 update [15, 16], TNFbs should be initiated in patients with a definite diagnosis of r-axSpA [usually identified by the fulfilment of the modified New York (mNY) criteria] [17], presenting with an active disease and a positive expert's opinion, despite NSAID treatment. Also, these recommendations suggest consideration of discontinuation of TNFb treatment in the case of insufficient response after 6–12 weeks of treatment.

The 2010 update [18] of these recommendations included the major change that not only r-axSpA patients could be treated with TNFb, but also all patients fulfilling the ASAS axial SpA criteria, and the previous NSAID treatment duration was shortened.

In the most recent update (2016) [19], no major changes were included with regard to TNFb initiation in axSpA patients, but (for the first time) an active disease could be defined either by a BASDAI or by an Ankylosing Spondylitis Disease Activity Score (ASDAS).

Finally, the marketing authorization for the initiation of TNFbs by the European Medicines Agency (EMA) includes either severe r-axSpA with inadequate response to conventional therapy, or severe non-radiographic axSpA but with objective signs of inflammation. (Supplementary Table S1, available at *Rheumatology* online, summarizes the 2003/2006, 2016 and EMA recommendations.)

However, we know that a gap exists between recommendations and their implementation in clinical practice: potentially, neither all patients meeting the conditions for TNFb initiation will be prescribed a TNFb, nor all patients for whom a TNFb is prescribed will fully meet these conditions. To date, there are some reported studies in RA that conclude that 22.8% of patients adhere to treatment recommendations (concerning DMARDs therapy) [20]. However, there is no data regarding the adherence to TNFb recommendations for ax-SpA management in daily clinical practice, nor for the long-term impact of such adherence.

These preliminary remarks prompted us to conduct this study aiming: to describe adherence to the 2003/2006 ASAS, 2016 ASAS/EULAR and EMA recommendations for TNFb initiation and its impact on functional disability, quality of life and sick-leave days over 5 years of follow-up; to describe adherence to the 2003/2006 ASAS and 2016 ASAS/EULAR recommendations for TNFb continuation and its impact on functional disability, quality of life and sick-leave days over 5 years of follow-up.

## Methods

### Study design

Data from the DESIR cohort (NCT01648907), the French prospective cohort of patients with early inflammatory back pain suggestive of axSpA was used [21]. Visits were scheduled every 6 months during the first 2 years and yearly thereafter. The present study analyses only the first 5 years of follow-up, and for the study we obtained the approval of the 'Comité pour la Protection des Personnes Physiques (CPP) île de France – III' ethical committee. All participants gave their written informed consent.

### Patients

A total of 708 patients aged >18 and <50 years old with early inflammatory back pain (>3 months but <3 years) suggestive of ax-SpA were included in this study. Previous biologic treatment was an exclusion criterion of the cohort; therefore, no patient had been exposed to TNFbs at baseline. Patients who received a biologic agent other than a TNFb as the first biologic treatment were also excluded. The dataset used for this study was locked on 15 June 2016.

### Visits definition

TNFbs could be initiated at any time during the follow-up, according to a patient's rheumatologist's decision, including between two visits. In order to evaluate the criteria fulfilment for TNFb initiation according to recommendations for TNFb initiation, V0 was defined as the last visit available before TNFb initiation. Adherence to recommendations for TNFb initiation (i.e. whether a patient who met the conditions for initiating a TNFb at V0 had indeed received a TNFb) was evaluated at the first available visit following V0 (i.e. at the V1 visit); when this visit occurred at least 12 weeks after TNFb initiation, evaluation of whether the patient met the conditions for continuing TNFb treatment was also conducted at this visit. Finally, adherence to recommendations for TNFb continuation (e.g. whether a patient who met the conditions for continuing a TNFb at the V1) was evaluated at the next available visit, i.e. V2.

For patients not receiving TNFb therapy during the 5 years of follow-up, we checked whether they had met the conditions for initiating a TNFb at any visit. For patients who did, this visit was considered V0; for patients who did not, any visit could be considered V0. For patients/visit balance concerns, we decided to look at the distribution of V0 across patients commencing TNFb therapy and to attribute V0 proportionally for patients who did not (e.g. for 162 patients who commenced a TNFb, V0 was the inclusion visit; so, we considered the inclusion visit as V0 for 162 patients who did not commence the therapy).

### Data collection

Socio-demographics included age, gender, highest degree of education, centre of inclusion (with ⩾30

patients including in DESIR cohort), smoking status and days of sick leave between each visit. Regarding disease characteristics, ASAS and mNY criteria [17, 22], presence of inflammatory lesions on MRI, HLA-B27 status, level of confidence of the Rheumatologist $\geqslant 7$ (0–10 scale) in the axSpA diagnosis, abnormal CRP (defined as $\geqslant 6$ mg/dl) and NSAIDs intake were collected. Disease activity was assessed by the BASDAI, ASDAS [23] and the BAS-G [24]. Disease severity was evaluated by the BASFI [25] and BASMI [26]. We assessed quality of life through the Short Form-36 (SF-36) [27].

*Assessment of recommendations*

A description of the different sets of recommendations and their equivalence to the variables collected in DESIR is presented in supplementary Table S2, available at *Rheumatology* online.

Regarding recommendations for TNFb initiation, 2003/2006 ASAS recommendations propose that therapy should be initiated in patients with: definite diagnosis of radiographic axSpA according to the mNY criteria, AND presenting with an active disease for at least 4 weeks, defined by a BASDAI $\geqslant 4$ (on a 0–10 scale), AND a positive expert's opinion, AND despite conventional therapy (failure of at least two NSAIDs over a 3 months' period at maximum recommended dose unless contraindicated was mandatory). According to the ASAS/EULAR 2016 recommendations for TNFb initiation, these drugs should be initiated in patients with: objective abnormalities of the sacroiliac joints (either according to the mNY *OR* MRI sacroiliitis) *OR* elevated CRP, AND NSAID inefficacy (at least two NSAIDs over 4 weeks at maximum recommended dose), AND presenting with an active disease for at least 4 weeks, defined by a BASDAI $\geqslant 4$ (in a 0–10 scale) *OR* by ASDAS $\geqslant 2.1$, AND a positive expert's opinion. Finally, according to EMA recommendations for TNFb initiation, therapy should be initiated in patients with: severe AS with inadequate response to conventional therapy *OR* severe non-radiographic axSpA with objective signs of inflammation (defined by elevate CRP and/or MRI).

Regarding recommendations for TNFb continuation, 2003/2006 ASAS recommendations propose that therapy should be continued in patients with: a BASDAI 50% relative change *OR* an absolute change of 20 points (0–100 scale) after 6–12 weeks of treatment. According to the 2016 ASAS/EULAR recommendations for TNFb continuation, these drugs should be continued in patients with: an ASDAS improvement $\geqslant 1.1$ *OR* a BASDAI improvement $\geqslant 2$ (0–100 scale) after at least 12 weeks of treatment.

### Handling of missing data

All missing information was carried forward from the previous visit, except for longitudinal outcomes, which were estimated by mixed-model estimation. For imaging variables, missing information was considered to be negative.

### Statistical analysis

First, a description of the use of TNFbs over the first 5 years of follow-up at each DESIR cohort visit and the baseline characteristics of groups of patients commencing/not commencing TNFb therapy was performed.

The percentages of patients meeting the conditions for TNFb initiation according to ASAS 2003/2006, 2016 and EMA recommendations within the group of patients commencing TNFb therapy, and also within the group of patients not commencing TNFb therapy, were calculated. We evaluated the percentage of patients adherent to each recommendation for TNFb initiation: a patient was considered adherent to recommendations if he/she met the conditions for initiating a TNFb (at V0) and who commenced TNFb therapy between V0 and V1, or if he/she did not meet the conditions for TNFb initiation at V0 and did not commence TNFb therapy between V0 and V1. Identification of the predictive factors for the adherence to each TNFb initiation recommendation were explored first by univariable analysis (Chi-square and *t* test, as appropriate), and thereafter by multivariate logistic regression, including in the model variables selected by the univariate analysis (when $P \leqslant 0.20$). Finally, we explored the impact of adherence to each recommendation for TNFb initiation by estimating disease severity (i.e. BASFI), quality of life and days of sick leave over 5 years by mixed models with random effects (here, the subject) and including in the model 'adherence' as the fixed independent variable.

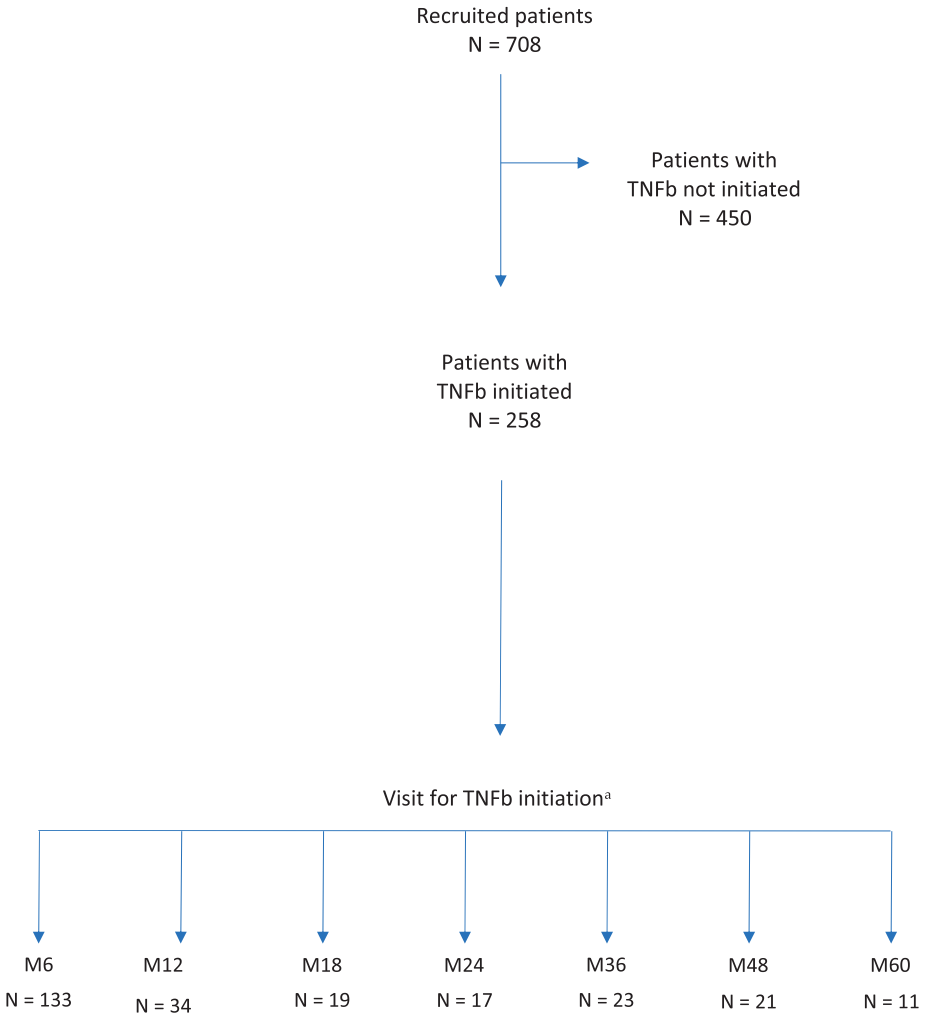
Regarding recommendations for TNFb continuation, the percentage of patients meeting the conditions for TNFb continuation at V1 (according to ASAS 2003/2006 and 2016 recommendations) within the group of patients who commenced TNFb therapy were calculated. We evaluated the percentage of patients adherent to each recommendation for TNFb continuation: a patient was considered adherent if at V1 he/she met the conditions for continuing TNFb therapy and at the following visit (V2) he/she was still on TNFb therapy, but also if he/she did not meet the conditions for continuing at V1 and at V2 TNFb treatment had been discontinued. Identification of the predictive factors for the adherence to each TNFb continuation recommendation were explored first by univariable analysis (Chi-square and *t* test, as appropriate), and thereafter by multivariate logistic regression, including in the model variables selected by the univariate analysis (when $P \leqslant 0.20$). Finally, we explored the impact of adherence to each recommendation for TNFb continuation by estimating disease severity (i.e. BASFI), quality of life and days of sick leave over 5 years by binomial mixed models with random effects (here, the subject) and including in the model 'adherence' as the fixed independent variable.

The data were analysed using the software SPSS 20.0 version and R version 3.2.3.

## Results

Of the 708 patients included in the analysis, a total of 258 (36.44%) patients commenced TNFb therapy over the first 5 years of follow-up. A flow chart is presented in Fig. 1.

**Fig. 1** Flow chart of the analysis




[a]no patient was exposed to TNFb at baseline (M0).
*M*: month. *TNFb*: TNF α blockers.

Demographics and disease characteristics of all patients at inclusion in the cohort are presented in Table 1.

## Recommendations for TNFb initiation

Fig. 2 and supplementary Fig. S1, available at *Rheumatology* online, show Venn diagrams representing the number of patients meeting the conditions required for each recommendation (ASAS 2003/2006, 2016 and EMA) for TNFb initiation. Of the 258 patients who initiated a TNFb, 30 patients (11.63%), 83 (32.17%) and 175 patients (67.83%) met the conditions for TNFb initiation according to ASAS 2003/2006, 2016 and EMA recommendations, respectively. Of the group of patients who never initiated TNFb therapy, a total of 40 patients (8.89%), 144 (32.00%) and 290 patients (64.44%) met the conditions for TNFb initiation according to ASAS 2003/2006, 2016 and EMA recommendations, respectively, at least at one visit.

Of all the patients, 440 (62.15%), 389 (54.94%) and 335 (47.32%) patients were considered adherent (i.e. either commenced TNFb therapy when conditions were met or did not commence TNFb therapy when conditions were not met) to ASAS 2003/2006, 2016 and EMA recommendations, respectively.

Baseline demographic and disease characteristics with regard to recommendations adherence are represented in Table 2 and supplementary Table S3, available at *Rheumatology* online. Patients adhering to ASAS 2003/2006 recommendations for TNFb initiation were more frequently males [49.5% *vs* 40.7%, odds ratio (OR) 1.45, 95% CI: 1.07, 1.98] and had more frequently university studies (62.0%, *vs* 53.7%, OR = 1.43, 95% CI: 1.05, 1.95). Similarly, patients adhering to 2016 recommendations were more frequently males (50.4% *vs* 41.1%, OR = 1.46, 95% CI: 1.08, 1.96). No significant factors were found to be associated for EMA recommendations adherence.

The impact of adherence to recommendations for TNFb initiation over 5 years of follow-up is represented in Table 3 and in supplementary Table S4, available at *Rheumatology* online. Patients who were adherent to the ASAS 2003/2006 recommendations for TNFb initiation showed

**Table 1** Demographic data and baseline disease characteristics of the 708 patients from the DESIR cohort

| Demographic data and baseline characteristics | Total patients, *n* = 708 | Patients who initiated a TNFb over follow-up, *n* = 258 | Patients who did not initiate a TNFb over follow-up, *n* = 450 |
|---|---|---|---|
| Age ⩾40 years old | 202 (28.2) | 78 (30.2) | 124 (27.6) |
| Gender (male) | 327 (46.2) | 113 (43.8) | 214 (47.6) |
| High level of education (Univ.) | 417 (58.9) | 133 (51.6) | 284 (63.1) |
| Centre with 30 or more patients included | 488 (68.9) | 172 (66.7) | 316 (70.2) |
| Current smoking | 256 (36.2) | 99 (38.4) | 157 (34.9) |
| HLA-B27+ | 410 (57.9) | 147 (57.0) | 263 (58.4) |
| Level of confidence ⩾7/10 in SpA diagnosis | 548 (77.4) | 195 (75.6) | 353 (78.4) |
| X-ray mNY criteria fulfilling[a] | 175 (24.7) | 70 (27.1) | 105 (23.3) |
| ASAS criteria fulfilling | 449 (63.4) | 169 (65.5) | 280 (62.2) |
| MRI inflammatory lesions[a] | 271 (38.3) | 116 (45.0) | 155 (34.4) |
| Two or more NSAIDs intake | 464 (65.5) | 171 (66.3) | 293 (65.1) |
| CRP ⩾6 mg/dl | 330 (46.6) | 128 (49.6) | 202 (44.9) |
| BASDAI, 0–100, mean (S.D.) | 45.55 (20.84) | 55.26 (17.25) | 39.99 (20.69) |
| BASFI, 0–100, mean (S.D.) | 30.73 (23.61) | 40.14 (22.74) | 25.33 (22.39) |
| BASMI, 0–10, mean (S.D.) | 2.37 (0.98) | 2.73 (1.09) | 2.16 (0.85) |
| BAS-G, 0–10, mean (S.D.) | 5.20 (2.63) | 6.23 (2.17) | 4.61 (2.69) |
| SF-36 mental component, 0–100, mean (S.D.) | 40.84 (11.65) | 37.05 (11.59) | 43.02 (11.13) |
| SF-36 physical component, 0–100, mean (S.D.) | 39.74 (9.55) | 35.72 (8.35) | 42.05 (9.45) |

All results are presented as mean *n* (%) unless otherwise stated. Percentages indicate number of patients with the covariate from the total number of patients in each category. [a]mNY criteria and MRI inflammatory lesions according to the local investigator. ASAS: Assessment of SpondyloArthritis International Society; mNY: modified New York criteria; TNFb: TNF α blockers; Univ.: University.

significantly lower levels in BASFI [19.6 (19.9) *vs* 31.3 (23.1); $P < 0.001$], higher SF-36 score [45.0 (10.7) *vs* 41.0 (11.7) and 44.5 (9.2) *vs* 39.4 (9.4) for the mental and physical components, respectively, $P < 0.001$] and fewer days of sick leave [8.7 (39.7) days *vs* 24.4 (54.8) days in adherent *vs* not adherent patients, respectively, $P < 0.001$] over the 5 years of follow-up. These results were also found when exploring the impact of the adherence to the 2016 recommendations, in particular on days of sick leave: 10.7 (44.1) days *vs* 19.4 (58.4) days in adherent *vs* non-adherent patients, respectively, $P < 0.001$. No differences were found in these outcomes over the 5 years of follow up in patients adhering *vs* not adhering to the EMA recommendations.

### Recommendations for TNFb continuation

Of the 258 patients who commenced TNFb therapy over the 5 years of follow-up, 232 (93.93%) continued treatment at V2; of these, a total of 110 (47.41%) and 115 (49.57%) met the conditions for continuing TNFb therapy according to the ASAS 2003/2006 and 2016 recommendations for TNFb continuation, respectively.

Adherence to TNFb continuation recommendations was observed in 47.37 and 49.39% for the 2003/2006 and 2016 recommendations, respectively.

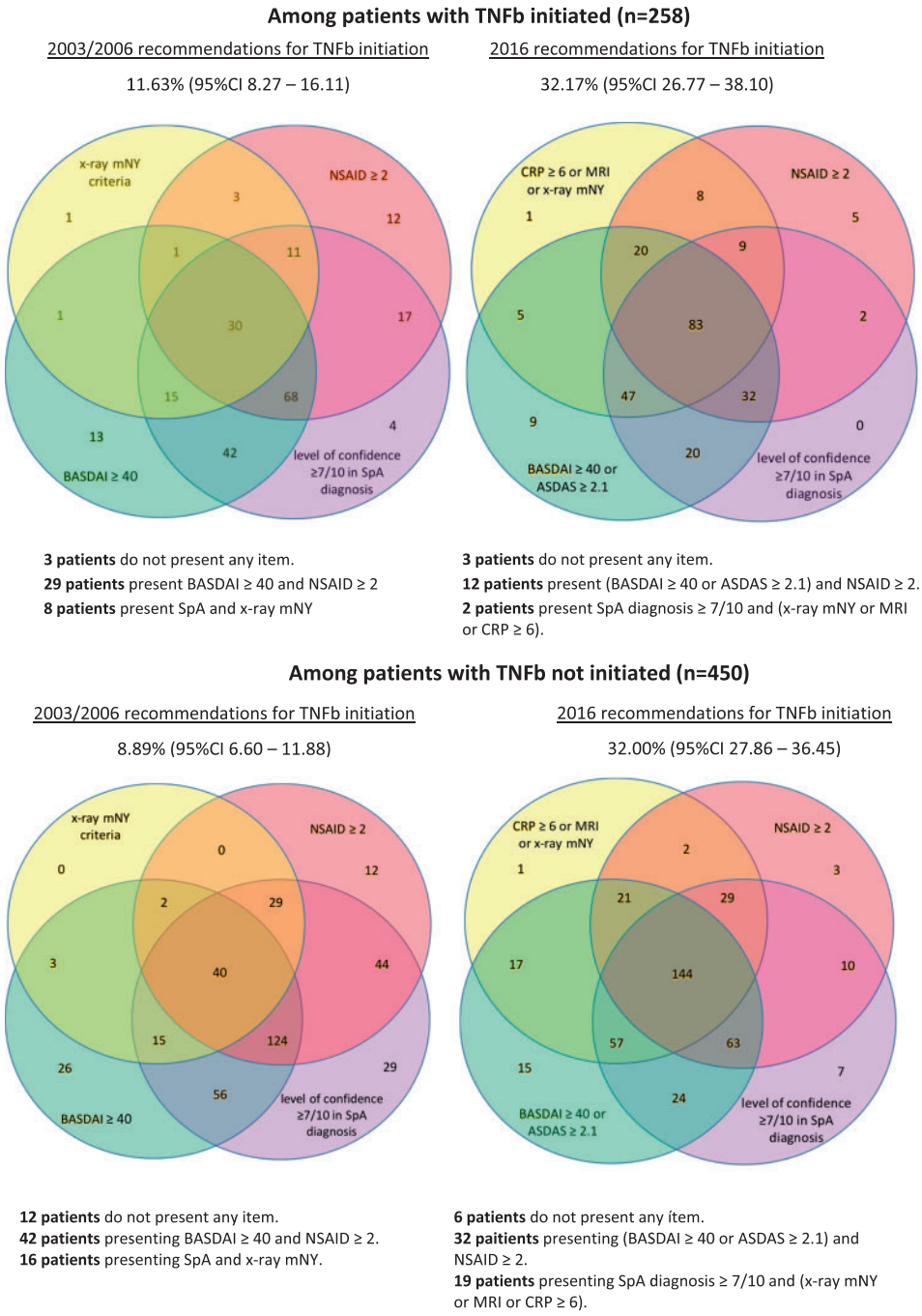
Patients adhering to 2003/2006 and 2016 recommendations for TNFb continuation were more frequently males (53.0% *vs* 34.6%, OR = 2.36, 95% CI: 1.93, 4.01 and 53.3% *vs* 33.6%, OR = 2.46, 95% CI: 1.45, 4.17, for 2003/2006 and 2016 recommendations, respectively) and had more frequently university studies (59.8% *vs* 44.6%, OR = 2.08, 95% CI: 1.23, 3.53 and 58.2% *vs* 45.6%, OR = 1.88, 95% CI: 1.11, 3.17, for 2006 and 2016 recommendations, respectively).

Table 4 represents the impact of adherence to recommendations for TNFb continuation over 5 years of follow-up. Better outcomes over follow-up [BASFI, SF-36 (mental and physical components) and in the number of days of sick leave] were found in the group of patients adhering to recommendations, in particular with regard to the days of sick leave; patients adhering to TNFb continuation recommendations presented a significant lower mean number of days of sick leave over the 5 years of follow-up [20.9 (57.7) *vs* 31.8 (76.5) days, $P < 0.001$ and 21.6 (59.7) days, against 31.6 (75.7) days, $P < 0.001$, for 2006 and 2016 recommendations, respectively].

## Discussion

This is, to our knowledge, one of the first studies aiming to evaluate adherence to recommendations for TNFb management in axSpA in daily clinical practice. These results highlight that a gap does indeed exist between the recommendations and their implementation in clinical practice. However, even though in our study ∼50% of patients were adherent to recommendations in the early axSpA population, both for initiation and continuation of TNFb, those patients had greater long-term functionality, quality of life and functional and employment/economic benefits compared with non-adherent patients.

**Fig. 2** Venn diagrams representing the items for meeting the conditions for 2003/2006 and 2016 recommendations




The frequency of adherence to recommendations in these SpA patients was not particularly high, taking into account the importance of these drugs in terms of costs and health impact. Nevertheless, the percentage was higher than in some reported studies in RA, in which it was concluded that 22.8% of patients from the SPOIR cohort adhered to treatment recommendations (concerning DMARDs therapy); however, in the Etude et Suivi des POlyarthrites Indifférenciées Récentes (ESPOIR) cohort, recommendations adherence differed between centres, ranging from 11.4 to 40.3% [20]. One possible explanation regarding these percentages in SpA *vs* RA patients is that recommendations for DMARDs management in RA include a wider range of drugs and several treatment steps, which make them more challenging in terms of adherence [28].

Regarding the suitability of the recommendations for TNFb initiation, 2016 seem to better discriminate patients

**Table 2** Baseline demographic and disease characteristics regarding the adherence to 2003–06 and 2016 recommendations for TNFb initiation

| Baseline demographic and disease characteristics | 2003/2006 recommendations for TNFb initiation | | | | | | 2016 recommendations for TNFb initiation | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TNFb initiated | | TNFb not initiated | | TNFb initiation | | TNFb initiated | | TNFb not initiated | | TNFb initiation | |
| | Meet 2003/2006 conditions for initiation (a) *n* = 30 | Do not meet 2003/2006 conditions for initiation (c) *n* = 228 | Meet 2003/2006 conditions for initiation (b) *n* = 40 | Do not meet 2003/2006 conditions for initiation (d) *n* = 410 | Adherence to 2003/2006 rec. for initiation (a + d) *n* = 440 | No adherence to 2003/2006 rec. for initiation (b + c) *n* = 268 | Meet 2016 conditions for initiation (a) *n* = 83 | Do not meet 2016 conditions for initiation (c) *n* = 175 | Meet 2016 conditions for initiation (b) *n* = 144 | Do not meet 2016 conditions for initiation (d) *n* = 306 | Adherence to 2016 rec. for initiation (a + d) *n* = 389 | No adherence to 2016 rec. for initiation (b + c) *n* = 319 |
| Age ⩾40 years old | 7 (23.3) | 71 (31.1) | 12 (30.0) | 119 (29.0) | 126 (28.6) | 83 (31.0) | 20 (24.1) | 58 (33.1) | 30 (20.8) | 94 (30.7) | 114 (29.3) | 88 (27.6) |
| Gender (male) | 20 (66.7) | 93 (40.8) | 16 (40.0) | 198 (48.3) | 218 (49.5) | 109 (40.7) | 47 (56.6) | 66 (37.7) | 65 (45.1) | 149 (48.7) | 196 (50.4) | 131 (41.1) |
| High level of education (Univ.) | 16 (53.3) | 117 (51.3) | 27 (67.5) | 257 (62.7) | 273 (62.0) | 144 (53.7) | 40 (48.2) | 93 (53.1) | 89 (61.8) | 195 (63.7) | 235 (60.4) | 182 (57.1) |
| Centre with 30 or more patients included | 17 (56.7) | 155 (68.0) | 31 (77.5) | 285 (69.5) | 302 (68.6) | 186 (69.4) | 58 (69.9) | 114 (65.1) | 97 (67.4) | 219 (71.6) | 277 (71.2) | 211 (66.1) |
| Current smoking | 17 (56.7) | 82 (36.0) | 16 (40) | 135 (32.9) | 152 (34.5) | 98 (36.6) | 38 (45.8) | 61 (34.9) | 47 (32.6) | 110 (35.9) | 148 (38.0) | 108 (33.9) |
| HLA-B27+ | 23 (76.7) | 124 (54.4) | 30 (75.0) | 233 (56.8) | 256 (58.2) | 154 (57.5) | 54 (65.1) | 93 (53.1) | 98 (68.1) | 165 (53.9) | 219 (56.3) | 191 (59.9) |
| Level of confidence ⩾7/10 in SpA diagnosis | 30 (100.0) | 165 (72.4) | 40 (100.0) | 313 (76.3) | 343 (78.0) | 205 (76.5) | 83 (100.0) | 112 (64.0) | 144 (100.0) | 209 (68.3) | 292 (75.1) | 256 (80.3) |
| X-ray mNY criteria fulfilling[a] | 30 (100.0) | 40 (17.5) | 40 (100.0) | 65 (15.9) | 95 (21.6) | 80 (29.9) | 37 (44.6) | 33 (18.9) | 55 (38.2) | 50 (16.3) | 87 (22.4) | 88 (27.6) |
| ASAS criteria fulfilling | 29 (96.7) | 140 (61.4) | 37 (92.5) | 243 (59.3) | 272 (61.8) | 177 (66.0) | 65 (78.3) | 104 (59.4) | 111 (77.1) | 169 (55.2) | 234 (60.2) | 215 (67.4) |
| MRI inflammatory lesions[a] | 24 (80.0) | 92 (40.4) | 29 (72.5) | 126 (30.7) | 150 (34.1) | 121 (45.1) | 60 (72.3) | 56 (32.0) | 86 (59.7) | 69 (22.5) | 129 (33.2) | 142 (44.5) |
| Two or more NSAIDs intake | 30 (100.0) | 141 (61.8) | 40 (100.0) | 253 (61.7) | 283 (64.3) | 181 (67.5) | 83 (100.0) | 88 (50.3) | 139 (96.5) | 154 (50.3) | 237 (60.9) | 227 (71.2) |
| CRP ⩾6 mg/dl | 20 (66.7) | 108 (47.4) | 28 (70.0) | 174 (42.4) | 194 (44.1) | 136 (50.7) | 62 (74.7) | 66 (37.7) | 110 (76.4) | 92 (30.1) | 154 (39.6) | 176 (55.2) |
| BASDAI, 0–100, mean (s.d.) | 56.3 (12.5) | 55.1 (17.8) | 50.0 (14.6) | 39.0 (20.9) | 40.2 (20.9) | 54.3 (17.4) | 56.5 (17.1) | 54.7 (17.3) | 45.8 (16.7) | 37.3 (21.8) | 41.4 (22.3) | 50.7 (17.6) |
| BASFI, 0–100, mean (s.d.) | 29.9 (22.8) | 41.5 (22.4) | 33.1 (22.0) | 24.6 (22.3) | 24.9 (22.4) | 40.2 (22.5) | 36.8 (24.1) | 41.7 (21.9) | 28.6 (21.5) | 23.8 (22.7) | 26.6 (23.6) | 35.8 (22.7) |
| BASMI, 0–10, mean (s.d.) | 2.9 (1.3) | 2.7 (1.1) | 2.3 (0.9) | 2.1 (0.8) | 2.2 (0.9) | 2.6 (1.1) | 2.7 (1.15) | 2.8 (1.1) | 2.2 (0.9) | 2.1 (0.8) | 2.2 (0.9) | 2.5 (1.0) |
| BAS-G, 0–10, mean (s.d.) | 6.1 (1.9) | 6.2 (2.2) | 5.7 (2.3) | 4.5 (2.7) | 4.6 (2.7) | 6.2 (2.2) | 6.4 (2.1) | 6.1 (2.2) | 5.4 (2.3) | 4.2 (2.8) | 4.7 (2.8) | 5.8 (2.3) |
| SF-36 mental component, 0–100, mean (s.d.) | 36.7 (11.7) | 37.1 (11.6) | 40.5 (13.1) | 43.3 (10.9) | 42.8 (11.1) | 37.6 (11.9) | 37.7 (11.7) | 36.7 (11.5) | 42.4 (11.4) | 43.3 (11.0) | 42.1 (11.4) | 39.3 (11.8) |
| SF-36 physical component, 0–100, mean (s.d.) | 37.9 (8.8) | 35.4 (8.3) | 39.0 (7.6) | 42.3 (9.5) | 42.0 (9.6) | 35.9 (8.2) | 36.2 (8.5) | 35.5 (8.3) | 39.8 (8.0) | 43.1 (9.9) | 41.6 (10.0) | 37.4 (8.4) |

All results are presented as mean *n* (%) unless otherwise stated. Percentages indicate number of patients with the covariate from the total number of patients in each category. [a]mNY criteria and MRI inflammatory lesions according to the local investigator. ASAS: Assessment of SpondyloArthritis International Society; Univ.: University; mNY: modified New York criteria; rec.: recommendations; TNFb: TNF α blockers.

**Table 3** Impact of adherence to recommendations for TNFb initiation over 5 years of follow-up

| Disease severity, quality of life and sick leave | 2003/2006 recommendations for TNFb initiation | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | TNFb initiated | | | TNFb not initiated | | | TNFb initiation | | |
| | Meet 2003/2006 conditions for initiation (a) $n = 30$ | Do not meet 2003/2006 conditions for initiation (c) $n = 228$ | $P$-value[a] | Meet 2003/2006 conditions for initiation (b) $n = 40$ | Do not meet 2003/2006 conditions for initiation (d) $n = 410$ | $P$-value[b] | Adherence to 2003/2006 rec. for initiation (a + d) $n = 440$ | No adherence to 2003/2006 rec. for initiation (b + c) $n = 268$ | $P$-value[c] |
| BASFI over 5 years (0–100) | 23.8 (20.0) | 32.6 (23.1) | 0.020 | 23.6 (20.9) | 19.2 (19.8) | 0.200 | 19.6 (19.9) | 31.3 (23.1) | <0.001 |
| SF-36 mental component over 5 years (0–100) | 41.1 (11.6) | 40.9 (11.7) | 0.900 | 41.8 (11.9) | 45.3 (10.56) | 0.007 | 45.0 (10.7) | 41.0 (11.7) | <0.001 |
| SF-36 physical component over 5 years (0–100) | 42.6 (8.3) | 38.7 (9.3) | 0.007 | 43.5 (8.7) | 44.7 (9.2) | 0.500 | 44.5 (9.2) | 39.4 (9.4) | <0.001 |
| Sick leave over 5 years (days) | 15.1 (49.4) | 27.2 (69.0) | 0.100 | 8.1 (26.4) | 8.3 (38.8) | 0.900 | 8.7 (39.7) | 24.4 (64.8) | <0.001 |
| | 2016 recommendations for TNFb initiation | | | | | | | | |
| | TNFb initiated | | | TNFb not initiated | | | TNFb initiation | | |
| | Meet 2016 conditions for initiation (a) $n = 83$ | Do not meet 2016 conditions for initiation (c) $n = 175$ | $P$-value[a] | Meet 2016 conditions for initiation (b) $n = 144$ | Do not meet 2016 conditions for initiation (d) $n = 306$ | $P$-value[b] | Adherence to 2016 rec. for initiation (a + d) $n = 389$ | No adherence to 2016 rec. for initiation (b + c) $n = 319$ | $P$-value[c] |
| BASFI over 5 years (0–100) | 28.3 (23.3) | 33.2 (22.6) | 0.040 | 20.9 (20.0) | 19.0 (20.0) | 0.500 | 21.5 (21.3) | 27.8 (22.3) | <0.001 |
| SF-36 mental component over 5 years (0–100) | 41.8 (11.6) | 40.5 (11.7) | 0.300 | 45.4 (10.9) | 44.7 (10.6) | 0.600 | 43.9 (11.0) | 42.6 (11.6) | 0.003 |
| SF-36 physical component over 5 years (0–100) | 41.1 (9.1) | 38.2 (9.3) | 0.003 | 43.6 (8.7) | 45.1 (9.4) | 0.200 | 44.0 (9.5) | 40.6 (9.4) | <0.001 |
| Sick leave over 5 years (days) | 18.4 (55.0) | 29.3 (71.9) | 0.030 | 7.3 (31.7) | 8.7 (40.4) | 0.500 | 10.7 (44.1) | 19.4 (58.4) | <0.001 |

All results are presented as mean (S.D.). [a]Mixed model for (a) *vs* (c); [b]mixed model for (b) *vs* (d); [c]mixed model for (a + d) *vs* (b + c). Comp.: component; rec.: recommendations; TNFb: TNF α blockers.

**Table 4** Impact of adherence to recommendations for TNFb continuation over 5 years of follow-up

| Disease severity, quality of life and sick leave | 2006 recommendations for TNFb continuation | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | TNFb continued | | | TNFb discontinued | | | TNFb continuation | | |
| | Meet 2003/2006 conditions for continuation (a) $n = 106$ | Do not meet 2003/2006 conditions for continuation (c) $n = 126$ | $P$-value[a] | Meet 2003/2006 conditions for continuation (b) $n = 4$ | Do not meet 2003/2006 conditions for continuation (d) $n = 11$ | $P$-value[b] | Adherence to 2003/2006 rec. for continuation (a + d) $n = 117$ | No adherence to 2003/2006 rec. for continuation (b + c) $n = 130$ | $P$-value[c] |
| BASFI over 5 years (0–100) | 25.1 (21.6) | 37.0 (22.6) | <0.001 | 28.1 (23.7) | 40.2 (23.6) | 0.500 | 26.3 (22.1) | 36.9 (22.7) | <0.001 |
| SF-36 mental component over 5 years (0–100) | 42.7 (11.5) | 39.6 (11.4) | 0.003 | 37.0 (10.6) | 34.2 (11.1) | 0.500 | 42.0 (11.7) | 39.6 (11.4) | 0.002 |
| SF-36 physical component over 5 years (0–100) | 41.8 (9.3) | 36.5 (8.6) | <0.001 | 39.5 (9.9) | 38.0 (8.8) | 0.982 | 41.5 (9.3) | 36.6 (8.6) | <0.001 |
| Sick leave over 5 years (days) | 21.2 (58.9) | 32.5 (77.5) | 0.030 | 12.2 (25.2) | 17.3 (43.6) | 0.590 | 20.9 (57.7) | 31.8 (76.5) | 0.030 |
| | 2016 recommendations for TNFb continuation | | | | | | | | |
| | TNFb continued | | | TNFb discontinued | | | TNFb continuation | | |
| | Meet 2016 conditions for continuation (a) $n = 111$ | Do not meet 2016 conditions for continuation (c) $n = 121$ | $P$-value[a] | Meet 2016 conditions for continuation (b) $n = 4$ | Not meet 2016 conditions for continuation (d) $n = 11$ | $P$-value[b] | Adherence to 2016 rec. for continuation (a + d) $n = 122$ | No adherence to 2016 rec. for continuation (b + c) $n = 125$ | $P$-value[c] |
| BASFI over 5 years (0–100) | 26.0 (21.4) | 36.7 (23.2) | <0.001 | 28.1 (23.7) | 40.2 (23.6) | 0.500 | 27.1 (21.9) | 36.6 (23.2) | <0.001 |
| SF-36 mental component over 5 years (0–100) | 42.8 (11.4) | 39.4 (11.5) | 0.002 | 37.0 (10.6) | 34.2 (11.1) | 0.500 | 42.1 (11.6) | 39.4 (11.5) | 0.010 |
| SF-36 physical component over 5 years (0–100) | 41.3 (9.3) | 36.7 (8.7) | <0.001 | 39.5 (9.9) | 38.0 (8.8) | 0.982 | 41.1 (9.3) | 36.8 (8.8) | <0.001 |
| Sick leave over 5 years (days) | 22.0 (61.1) | 32.2 (76.7) | 0.049 | 12.2 (25.2) | 17.3 (43.6) | 0.590 | 21.6 (59.7) | 31.6 (75.7) | 0.042 |

All results are presented as mean (S.D.). [a]Mixed model for (a) *vs* (c); [b]mixed model for (b) *vs* (d); [c]mixed model for (a + d) *vs* (b + c). Comp.: component; rec.: Recommendations; TNFb: TNF $\alpha$ blockers.

who can benefit from these treatments. The fact that the ASAS 2003/2006 recommendations only can be applied in r-axSpA patients deprives a lot of patients with nr-axSpA of treatment. Concerning the percentage of adherence, the 2003/2006 recommendations show a slightly higher percentage of adherence at the expense of patients for whom TNFbs were not initiated when conditions were not met. This can be explained by the fact that the 2003/2006 recommendations are stricter than those from 2016 (i.e. in the 2003/2006 recommendations, patients may commence this treatment only if they have X-ray mNY criteria, in spite of a high disease activity); thus, the majority of them did not initiate treatment because they did not meet the conditions for initiation.

Interestingly, some baseline socio-demographic characteristics were strongly associated with adherence to recommendations for TNFb initiation: that is, being a male and having a higher level of education. These results are similar to those reported in previous studies in the DESIR cohort, in which these two characteristics are associated with stable low or improving disease activity trajectories [29]. In addition, male sex has been reported as a factor associated with better treatment adherence [30]. This may be a patient profile with greater likelihood of good response to treatment and, therefore, with greater adherence to the recommendations.

Recent reported studies showed that productivity loss costs among DESIR patients still represented between 10 and 17% of annual costs, and the most significant cost component was biologic drugs [31]. In our study, being in accordance with ASAS 2003/2006 and 2016 recommendations had a significant impact on employment and economic costs. That is to say, in spite of the higher cost of the biologic treatment in patients who adhered to the recommendations, selection of patients for the initiation of TNFb therapy according to the recommendations reduces days of sick leave and, as a consequence, potentially productivity loss costs.

Our study had some limitations but also several strengths. One limitation was that TNFb treatment could be initiated at any time by the treating rheumatologist, independent of DESIR's visits, which can also implicate a variance in treatment duration between patients. However, by setting the study visits (i.e. V0, V1 and V2) and performing a mixed model with random effects, we reduced the variance across treatment duration at the time of evaluation and the variance of the impact at 5 years of follow-up. Furthermore, these intervals reflect real life, in which it is difficult to evaluate treatment effect at precisely 12 weeks of TNFb therapy, due to time constraints. Another limitation was that the fulfilment of recommendations was not included in the DESIR's case report form; however, recommendations were evaluated for each patient through the combination of different variables, and all of them were available in the DESIR database.

The main strength of our study is that it is the first to evaluate the implementation of recommendations for the management of TNFb use in patients with ax-SpA in daily clinical practice over 5 years of follow-up, and analyses its impact regarding functional outcomes.

In conclusion, this study demonstrates that adherence to recommendations in the initiation and continuation of TNFb therapy leads to better long-term outcomes in terms of quality of life and sick leave.

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## Supplementary data

Supplementary data are available at *Rheumatology* online.

## References

1 Dougados M, Baeten D. Spondyloarthritis. Lancet Lond Engl 2011;377:2127–37.

2 Rudwaleit M, van der Heijde D, Landewe R *et al*. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011;70:25–31.

3 Van den Bosch F, Kruithof E, Baeten D *et al*. Effects of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor alpha (infliximab) in spondyloarthropathy: an open pilot study. Ann Rheum Dis 2000;59:428–33.

4 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.

5 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.

6 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.

7 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.

8 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.

9 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.

10 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.

11 Dougados M, van der 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.

12 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.

13 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.

14 Inman RD, Davis JC, Heijde Dvd *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.

15 Braun J, Pham T, Sieper J *et al*. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. Ann Rheum Dis 2003;62:817–24.

16 Braun J, Davis J, Dougados M *et al*. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. Ann Rheum Dis 2006;65:316–20.

17 van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.

18 van der Heijde D, Sieper J, Maksymowych WP *et al*. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann Rheum Dis 2011;70:905–8.

19 van der Heijde D, Ramiro S, Landewé R *et al*. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76:978–91.

20 Escalas C, Dalichampt M, Combe B *et al*. Effect of adherence to European treatment recommendations on early arthritis outcome: data from the ESPOIR cohort. Ann Rheum Dis 2012;71:1803–8.

21 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. Joint Bone Spine 2015;82:345–51.

22 Rudwaleit M, van der Heijde D, Landewe R *et al*. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777–83.

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 Jones SD, Steiner A, Garret SL *et al*. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). J Rheumatol 1996;35:66–71.

25 Calin A, Garret 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.

26 Jones SD, Porter J, Garret SL *et al*. A new scoring system for the Bath Ankylosing Spondylitis Metrology index (BASMI). J Rheumatol 1995;22:1609.

27 Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. BMJ 1993;306:1437–40.

28 Smolen JS, Landewé R, Breedveld FC *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492–509.

29 Moltó A, Tenezas du Montcel S, Wendling D *et al*. Disease activity trajectories in early axial spondyloarthritis: results from the DESIR cohort. Ann Rheum Dis 2017;76:1036–41.

30 Wallman JK, Kapetanovic MC, Petersson IF *et al*. Comparison of non-radiographic axial spondyloarthritis and ankylosing spondylitis patients – baseline characteristics, treatment adherence, and development of clinical variables during three years of anti-TNF therapy in clinical practice. Arthritis Res Ther 2015;17:378.

31 Harvard S, Guh D, Bansback N *et al*. Costs of early spondyloarthritis: estimates from the first 3 years of the DESIR cohort. RMD Open 2016;2:e000230.