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Drug maintenance of a second tumor necrosis factor alpha inhibitor in spondyloarthritis patients: a real-life multicenter study

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ABSTRACT

Objectives: Five TNF inhibitor (TNFi) agents are marketed for spondyloarthritis (SpA): 1 soluble receptor (SR) and 4 monoclonal antibodies (mAbs). From 15% to 30% of patients stop the first TNFi in the first 2 years, but we lack recommendations on the choice of the second TNFi. The aim here was to assess drug survival of a second TNFi in SpA and its determinants.

Methods: This was a multicenter observational study of SpA patients who started a first TNFi in 2013 and 2014 and were followed to 2018. For the first and second TNFi, we retrospectively collected data on initiation and discontinuation dates, type of TNFi, and reasons for withdrawal. Kaplan–Meier plots and log-rank tests were used to compare drug survival. Factors associated with drug survival of the second TNFi were analyzed by univariate Cox regression analyses.

Results: We included 244 patients. During a follow-up of 7,838 patient-months, 101 (41%) received 1 TNFi, and 143 (59%) switched to a second TNFi. Mean drug intake duration was significantly greater with the first than second TNFi: 21.7 (SD 19.6) and 15.4 (SD 13.6) months ($p<0.001$). When switching to another mAb or from an SR to an mAb (or the reverse), mean drug survival did not differ: 14.4 (SD 12.7) and 16 (SD 14.1) months ($p=0.35$). Factors associated with retaining the second TNFi were male sex ($p=0.054$) and age < 41 years at SpA diagnosis ($p=0.022$). On multivariable analysis, only age <41 years at diagnosis remained independently associated with maintenance of the second TNFi.

Conclusion: In SpA patients, drug survival is significantly longer with the first than second TNFi. Male sex and age <41 years at diagnosis were associated with retaining the second TNFi.

Key words: TNF inhibitors, spondyloarthritis, drug survival

1. Introduction

Spondyloarthritis (SpA) represents chronic inflammatory diseases that mainly affect the axial skeleton but can also involve peripheral joints (1). Treatment with tumor necrosis factor- α inhibitor (TNFi) agents greatly ameliorates axial and peripheral symptoms in patients with high disease activity despite treatment with non-steroid anti-inflammatory drugs (NSAIDs) and/or disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate or sulfasalazine (2–5). To date, 5 TNFi agents are marketed for active SpA in France: 1 soluble receptor (SR) of TNF (etanercept), and 4 monoclonal antibodies (mAbs; infliximab, adalimumab, golimumab and certolizumab).

These 5 TNFi agents have a comparable efficacy in first-line treatment. However, 15% to 32% of patients show inadequate response (lack of efficacy or safety issues) within the 2 years after starting the first TNFi. We lack recommendations on the choice of a second-line TNFi (2,3,6,7). Moreover, across published studies, predictors of a switch to a second TNFi are controversial. Sex, age, C-reactive protein (CRP) level, and disease activity may play a role in retention rate of a second TNFi course (8–10).

The aim of this study was to assess, in clinical daily practice, drug survival of a second TNFi in SpA and its determinants.

2. Methods

We conducted a multi-center, retrospective observational study in 3 cities (Tours, Orleans, Blois) in the Centre-Val de Loire state of France.

Study population and follow-up

SpA patient recruitment was previously described (11). Briefly, all rheumatologists who collaborated with 3 public hospitals in the Centre-Val de Loire area were asked to participate in the study via a mailed information letter. After their agreement, they provided the list of SpA patients who started their first TNFi in 2013 or 2014. To ensure the completeness of patient recruitment, we also used the list of patients seen during an educational visit before TNFi initiation (available in Tours and Orleans centers). Each patient received an information letter, with the possibility of refusing participation in the study. We excluded patients who participated in another clinical study.

2.1. Assessment of drug survival

Patients who agreed to participate were followed by academic or private practice rheumatologists from the date of starting the first TNFi until the end of the first trimester of 2018.

2.2. Predictors of retaining the second-line TNFi

Data were retrospectively collected from medical charts by using a standardized case report form. We collected data on demographics (age, sex, smoking status), SpA phenotype, date of diagnosis, human leukocyte antigen B27 (HLAB27) status, Assessment of SpondyloArthritis Society (ASAS) and modified New York (NYm) classification criteria (12–14), and disease activity at the start and end of TNFi courses or follow-up (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], CRP level). For each TNFi course, we collected the type of TNFi, dates of initiation and discontinuation, dosage, and route of administration; CRP level and BASDAI at initiation, 12 to 16 weeks after initiation and at withdrawal; methotrexate and NSAID concomitant treatments; and reason for TNFi discontinuation (lack of treatment effect, side effects, and remission).

Lack of treatment effect was defined as primary failure in case of lack of clinical improvement without any improvement described in the medical chart. Secondary failure was defined as lack of efficacy after clinical improvement recorded in the medical chart.

The study protocol was approved by the Committee for the Protection of Persons of Poitiers in June 2017.

2.3. Statistical analysis

Data for patients are described with numbers (%) for categorical variables and mean (standard deviation [SD]) for continuous variables. Patients were divided into 2 groups: receiving only 1 TNFi and receiving 2 TNFi courses during follow-up. Drug survival was calculated as the number of months treatment was maintained with the first and second TNFi courses. For each treatment course, start dates were the date of the first given dose and the stop date was the date of withdrawal recorded in the medical chart. For patients who switched to a second TNFi, we analyzed those who switched from an SR to an mAb or the reverse and those who switched from an mAb to another mAb. Kaplan–Meyer survival analysis and the log-rank test were used to compare drug survival.

Univariate Cox regression analysis, with age as a time scale, was used to identify potential factors associated with survival of the second TNFi at the end of follow-up and potential

confounding factors. Then, multivariable Cox regression analysis was used to introduce in the models factors associated with drug retention with $p < 0.20$ on univariate Cox regression analysis. Results are given in hazard ratios (HRs) with 95% confidence intervals (CIs). In case of missing data for repeated measurements (BASDAI, CRP level), the last observation carried forward method was used. $P < 0.05$ was considered statistically significant. Statistical analyses involved use of SAS v9.4 (SAS Inst. Inc., Cary, NC, USA).

3. Results

3.1. Study population and baseline characteristics.

Among the 274 SpA patients included, 30 were excluded: 23 with missing data and 7 refusals (Figure 1). Analyses involved 244 patients who were followed by 49/57 rheumatologists solicited for participation in this study. The mean follow-up was 32.1 (SD 18.8) months (total follow-up 7,838 patient-months). Patient characteristics are in the supplemental file [Appendix A, Table S1; See the supplementary material associated with this article online]: mean age at the start of the first TNFi was 45.1 (SD 12.5) years; 157 (64.6%) patients were women and 190 (78%) fulfilled ASAS or mNY classification criteria. The most common SpA phenotype was axial radiographic ($n = 117$, 47.9%) and 106 (52.2%) patients were HLAB27-positive. Among the 244 patients, 143 (59%) received a second TNFi and 101 (41%) received only one course of TNFi. At the end of follow-up, 56 (23%) patients continued their first TNFi (Figure 1).

Among the 101 patients who received only one TNFi, 77 (76.2%) received an mAb and 24 (23.8%) an SR; 77 (76.2%) fulfilled ASAS classification criteria, 15/44 (34.1) were current smokers, and 56 (55.4%) received concomitant NSAIDs and 22 (22%) concomitant methotrexate.

Among the 143 patients who switched to a second TNFi, 112 (78.3%) fulfilled ASAS classification criteria and 28/74 (37.8%) were current smokers; 55 (38.5%) switched from an mAb to another mAb and 88 (61.5%) from an SR to an mAb or the reverse (50 from mAb to SR and 38 from SR to mAb). Characteristics of these patients are in Table 1. The main reason for withdrawal of the first TNFI was secondary lack of efficacy (44%, $n=63$), then primary lack of efficacy (37.7%, $n=54$) and finally adverse events (17.6%, $n=25$) (Table 1).

Drug survival of the first TNFi

The mean duration of the first TNFi was 21.7 months (SD 19.6; median 11.6 [Q1–Q3 5.1–40.6]), with no difference according to the mode of action (SR or mAb, 19 and 22.7 months respectively, $p=0.0992$).

3.2. Drug survival of the second TNFi

Mean drug survival of the second TNFi was 15.4 months (SD 13.6; median 10.8 [Q1–Q3 4.9–22.9]). The drug survival was shorter for the second than first TNFi (mean difference 6.3 months, $p<0.001$). With a switch from one mAb to another mAb, mean drug survival was 14.4 (SD 12.7) months. With a change in mode of action between the first and second TNFi (mAb to SR or vice versa), mean drug survival was 16.0 (SD 14.1) months. The difference was not statistically significant ($p=0.3541$) (Figure 2). Appendix A, Figure S1, shows Kaplan-Meier survival curves for the second TNFi for the 3 possible switches: 1) mAb → mAb, 2) mAb → SR, 3) SR → mAb. The mean therapeutic duration of the second TNFi was 15.8 (SD 14.8) months, 16.4 (SD 13.3) months and 14.4 (SD 12.7) months for patients who switched from an mAb to SR, SR to mAb, and mAb to another mAb, respectively, with no significant difference between the 3 groups ($p=0.4700$, log rank test).

Regarding drug survival, a sensitivity analysis was performed by excluding patients who did not fulfill ASAS or mNY classification criteria ($n=54$). Thus, analyses were performed on 190 patients with similar characteristics to the overall population: 72 were men (38%), 93/163 were positive for HLAB27 and the mean age at SpA diagnosis was 40.9 (SD 13.1) years. Among the 190 patients, 78 (41%) and 112 (59%) received only 1 TNFi or a second TNFi, respectively; 43/112 (38.4%) switched from an mAb to another mAb, 29 (26%) from an SR to an mAb and 40 (35.6%) from an mAb to an SR. The mean duration of the second TNFi was 15.2 months (SD 13.4; median 10.9 [Q1–Q3 4.9–22.7]), identical to that in the overall population. As a second TNFi, 72 (64.3%) patients received an mAb, mainly adalimumab (36/72, 50%). Survival curves for the second TNFi by type of switch are in the appendix A (Figures S2 and S3). We found no significant difference in drug survival (log-rank tests). Thus, the results for drug survival, restricted to SpA patients fulfilling ASAS or mNY criteria, were consistent with data for the overall cohort.

For patients who stopped the first TNFi for lack of efficacy (N=137), mean drug survival was 15.8 (SD 14.8) months with a switch from an mAb to an SR and 16.4 (SD 13.3) months with a switch from an SR to an mAb (Figure 3). For patients who switched from an mAb to another mAb, the drug survival was shorter (mean 14.4 [SD 12.7] months), but the difference was not statistically significant ($p=0.47$).

The drug survival of the second TNFi was not affected by the mode of action or type of TNFi ($p=0.7301$ and $p=0.1674$) or reason for withdrawal of the first TNFi (mean primary failure: 14.6 months; secondary failure: 15.1 months; side effects: 18.2 months, $p=0.3520$) (Figure 4).

3.3. Determinants of drug survival of the second TNFi

On univariate Cox regression, drug survival of the second TNFi was longer with age < 41 versus > 50 years (HR=10, 95% CI 1.386-72.25, $p=0.0224$), with a trend for male sex ($p=0.0541$). Drug survival did not differ by SpA phenotype, HLAB27 status, smoking status, reason for withdrawal of the first TNFi, meeting ASAS or mNY criteria, baseline CRP level, BASDAI, concomitant use of methotrexate or NSAID, duration or mode of action of the first TNFi and symptoms duration (Appendix A, Table S2).

On multivariate Cox regression, including sex, age at SpA diagnosis and centre, age < 41 years at diagnosis remained a predictor of long drug survival of the second TNFi (HR=7.5, 95% CI 0.99-57.4, $p=0.014$) but not male sex (HR=1.8, 95% CI 0.7-4.5).

4. Discussion

In our observational study, 244 patients with SpA were followed for a mean of 32 months after the start of the first TNFi. Patient characteristics were consistent with French published data regarding spondyloarthritis (15,16). The mean duration of the first TNFi was 21.7 months, with no significant difference by TNFi mode of action. Among 244 SpA patients, 143 (59%) received a second TNFi. Mean drug survival was significantly shorter with the second than first TNFi (15.4 months). Drug survival of the second TNFi was not affected by sex, symptoms duration, reason for withdrawal of the first TNFi, change of mode of action, SpA phenotype, HLAB27 or smoking status, or classification criteria. Only age < 41 years at SpA diagnosis was significantly associated with retaining the second TNFi.

Regarding the drug survival of the first TNFi, retention rates vary among countries, probably because of the restriction and recommendations of national drug agencies. In an Australian observational study, 12% of patients with SpA changed the TNFi at 1 year after initiation of the first TNFi (17). In the ATTRA registry, duration rates for the first TNFi were 84% at 1 year, 76% at 2 years and 72% at 3 years, better than those reported for rheumatoid arthritis (10). In a Korean study, 26% of patients changed their first TNFi to another at 57.2 months of follow-up (18). In this previous study, the first TNFi prescribed was infliximab, then etanercept and adalimumab, unlike in our study, in which the first TNFi prescribed was, in descending order of frequency, adalimumab, etanercept, golimumab and infliximab, which can be explained by the fact that in France, we use mainly subcutaneous forms first (for economic reasons and common clinical practice). In a French study conducted in Auvergne (19), the mean duration of the first TNFi was 69.7 months, which was longer than in our study (21.7 months). In this previous retrospective study, the recruitment period was longer (2001 to 2015) than in our study (from 2013 and 2014). Fewer therapeutic options were available for patients with SpA in the 2000s, which encouraged rheumatologists to maintain the current treatment as long as possible. A Korean study found longer mean duration (84 months) probably due to the recruitment period (from 2003 to 2011) and national recommendations (20).

In the Australian study (17), retention rates at 1 and 2 years were better with etanercept than infliximab or adalimumab: 83% of patients with etanercept were still receiving it at 1 year and 58% at 2 years. These results are similar to those of a Finnish study, finding drug survival better with etanercept and adalimumab than infliximab (9).

As in our study, other studies did not find any differences in duration of the first TNFi by mode of action of the TNFi (10).

Overall, 59% of our patients received a second TNFi. The reason for withdrawal of the first TNFi was secondary lack of efficacy (44%), followed by primary lack of efficacy (38%). These results are close to those found in the DANBIO registry: the first reason for withdrawal of the first TNFi was loss of efficacy (56%), then adverse events (27%) (21). In other observational studies, such as the ATTRA registry, the main reason for withdrawal was adverse events (30.4%) (10).

In the present study, drug survival was significantly shorter for the second than first TNFi, which was previously described in observational studies, showing poorer response with the second TNFi (9,21–26). Indeed, in the DANBIO register, the median duration was shorter for the second than first TNFi: 1.6 (95% CI 1.0-2.2) *versus* 3.1 (2.6-3.7) years (21). In the study

by Lie *et al.*, the retention rate was higher for the first than second TNFi: 76% and 67% at 1 year and 65% and 60% at 2 years of follow-up (22). The same results were found in psoriatic arthritis, with a median duration of 2.2 (95% CI 1.9-2.5%) years for the first TNFi and 1.3 (1.0-1.6) years for the second TNFi (23).

We found only one factor associated with drug survival of the second TNFi: age < 41 years at SpA diagnosis, after adjustment for centre and sex. Thus, the change in mode of action between the first and second regimen was not associated with better retention rate or duration of the second TNFi, even in patients who stopped the first TNFi for lack of efficacy. These results agree with those from Sparado *et al.* (27), finding no difference in drug survival rates of the second TNFi between patients who switched from infliximab to adalimumab or from etanercept to adalimumab (27). However, in the Auvergne study (19), drug survival was longer with a change from one mAb to another mAb than when switching from an SR to a mAb or the reverse.

In our study, sex, SpA phenotype, HLAB27 status, current smoking, fulfilling ASAS or NYM criteria, disease activity (BASDAI, CRP level), reason for withdrawal of the first TNFi and concomitant treatments (methotrexate and NSAIDs) did not affect drug survival of the second TNFi. Our findings may result from the lack of power of our study due to missing data for the 143 patients who received a second TNFi: BASDAI scores (58%), smoking status (50%), HLAB27 status (17%) and CRP level (66%). Nevertheless, the data in the literature are inconsistent on this point. As suggested by some published data, smoking could affect TNFi efficacy. The lack of power due to missing data on smoking status (close to 50%) may explain why tobacco exposure did not affect drug survival in our study. However, a recent study suggested that smoking may affect disease activity at 6 months in patients receiving an TNFi, with no significant association with drug survival (28).

In the study by Gulyas *et al.*, older age at initiation of the first TNFi (mean age 42.5 [SD 12.6] versus 38.8 [SD 11.2] years) was a risk factor for discontinuation (29).

In the ATTRA registry, BASDAI and duration of disease did not affect drug survival. However, female sex and biological inflammation were associated with discontinuation of the TNFi (10). In the DANBIO registry, only male sex, low BASFI, adalimumab treatment and infliximab as the first TNFi were associated with longer drug survival. CRP level at initiation, BASDAI, concomitant treatment with methotrexate, and reason for withdrawal of the first TNFi did not affect the drug survival of the second TNFi (21). However, in the Swiss register,

with primary failure of the first TNFi, the median duration of the second TNFi was 1.1 years, but in the event of secondary failure, it was 3.8 years ($p=0.003$) (30).

In psoriatic arthritis, male patients and those with low number of painful joints and low fatigue score retained their second TNFi longer, as did patients in whom the drug was introduced early (25). Other studies such as the Norwegian study based on data from the NOR-DMARD registry (26) showed a lack of effect of the reason for withdrawal of the first TNFi on duration of the second TNFi.

To our knowledge, this is the first study to examine the effect of a change in mode of action between the first and second TNFi on drug survival of the second TNFi in real life, with a good participation rate for rheumatologists and patients (89%). The list of patients who started their first TNFi in 2013 or 2014 was obtained from a therapeutic education register in Orleans and Tours centres. This process limits the bias in patient selection. The larger number of patients in Tours *versus* Orleans and Blois implied a “centre effect”, which we were able to adjust for in the multivariate Cox model. The number of patients was identical in the groups “change of mode of action” and “no change of mode of action,” which allowed for good comparability. The data collection was standardized to limit classification bias. The limitations of this study are related to memory bias and the number of missing data due to the retrospective design, which may have influenced the analysis of factors affecting the duration of the second TNFi, with potentially a lack of power.

This observational study in current practice confirmed better survival of the first than second TNFi in patients with SpA. We show no change in survival of the second TNFi according to a change or not in mode of action between the first and second TNFi. Also, few factors affected the survival of the second TNFi, only age < 41 years at diagnosis.

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Appendix A. Supplementary data

Supplementary data (Figure S1-S3, Table S1-S2) associated with this article can be found in the online version at ...

References

1. Claudepierre P, Wendling D, Breban M, Goupille P, Dougados M. Ankylosing spondylitis, spondyloarthropathy, spondyloarthritis, or spondylarthritis: what's in a name? *Joint Bone Spine* 2012;79:534-5.
2. Wendling D, Lukas C, Paccou J, et al. Recommendations of the French Society for Rheumatology (SFR) on the everyday management of patients with spondyloarthritis. *Joint Bone Spine* 2014;81:6-14.
3. Wendling D, Lukas C, Prati C, et al. 2018 update of French Society for Rheumatology (SFR) recommendations about the everyday management of patients with spondyloarthritis. *Joint Bone Spine* 2018;85:275-84.
4. 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.
5. Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2011;70:896-904.
6. Wendling D, Claudepierre P, Toussiro E, Streit G, Prati C, Ornetti P. Agents anti-TNF α et traitement des spondylarthropathies. *Médecine thérapeutique* 2007;13:6.
7. Dougados M, Braun J, Szanto S, et al. Continuous efficacy of etanercept in severe and advanced ankylosing spondylitis: results from a 12-week open-label extension of the SPINE study. *Rheumatology (Oxford)* 2012;51:1687-96.
8. 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.
9. Heinonen AV, Aaltonen KJ, Joensuu JT, et al. Effectiveness and Drug Survival of TNF Inhibitors in the Treatment of Ankylosing Spondylitis: A Prospective Cohort Study. *J Rheumatol* 2015;42:2339-46.
10. Pavelka K, Forejtová S, Stolfa J, et al. Anti-TNF therapy of ankylosing spondylitis in clinical practice. Results from the Czech national registry ATTRA. *Clin Exp Rheumatol* 2009;27:958-63.
11. Pereira-Gillion C, Marot M, Griffoul-Espitalier I, Andras L, Goupille P, Salliot C. Application of Recommendations Regarding the Use of Subcutaneous Tumor Necrosis Factor Inhibitors in Spondyloarthritis by Rheumatologists in Daily Practice. *J Rheumatol* 2018;45:491-7.
12. Rudwaleit M, van der Heijde D, Landewé 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.
13. Rudwaleit M, van der Heijde D, Landewé 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.
14. 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.
15. Saraux A, Guillemin F, Guggenbuhl P, et al. Prevalence of spondyloarthropathies in France: 2001. *Ann Rheum Dis* 2005;64:1431-5

16. Dougados M, D'Agostino MA, Benessiano J, et al. The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. *Joint Bone Spine*. 2011 Dec;78:598-603.
17. Nell-Duxneuner V, Schroeder Y, Reichardt B, Bucsics A. The use of TNF-inhibitors in ankylosing spondylitis in Austria from 2007 to 2009 - a retrospective analysis. *Int J Clin Pharmacol Ther* 2012;50(:867-72.
18. Lee J-W, Kang J-H, Yim Y-R, et al. Predictors of Switching Anti-Tumor Necrosis Factor Therapy in Patients with Ankylosing Spondylitis. *PLoS ONE* 2015;10:e0131864.
19. Soubrier M, Pereira B, Fan A, et al. Retention rates of adalimumab, etanercept, and infliximab as first- or second-line biotherapies for spondyloarthritis patients in daily practice in Auvergne (France). *Int J Rheum Dis* 30 août 2018;
20. Kang J-H, Park D-J, Lee J-W, et al. Drug survival rates of tumor necrosis factor inhibitors in patients with rheumatoid arthritis and ankylosing spondylitis. *J Korean Med Sci* 2014;29:1205-11.
21. Glinthorg B, Østergaard M, Krogh NS, et al. Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor α inhibitor therapy: results from the Danish nationwide DANBIO registry. *Ann Rheum Dis* 2013;72:1149-55.
22. 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.
23. Glinthorg B, Ostergaard M, Krogh NS, et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor α inhibitor therapy: results from the Danish Nationwide DANBIO Registry. *Arthritis Rheum* 2013;65:1213-23.
24. Kristensen LE, Lie E, Jacobsson LTH, et al. Effectiveness and Feasibility Associated with Switching to a Second or Third TNF Inhibitor in Patients with Psoriatic Arthritis: A Cohort Study from Southern Sweden. *J Rheumatol* 2016;43:81-7.
25. Deodhar A, Yu D. Switching tumor necrosis factor inhibitors in the treatment of axial spondyloarthritis. *Semin Arthritis Rheum* 2017;47:343-50.
26. Fagerli KM, Lie E, van der Heijde D, et al. Switching between TNF inhibitors in psoriatic arthritis: data from the NOR-DMARD study. *Ann Rheum Dis* 2013;72:1840-4.
27. Spadaro A, Punzi L, Marchesoni A, et al. Switching from infliximab or etanercept to adalimumab in resistant or intolerant patients with spondyloarthritis: a 4-year study. *Rheumatology (Oxford)* 2010;49:1107-11.
- 28 Yahya F, Gaffney K, Hamilton L, et al; for BRITSpA. Tumour necrosis factor inhibitor survival and predictors of response in axial spondyloarthritis-findings from a United Kingdom cohort. *Rheumatology (Oxford)*. 2018 ;57:619-624
29. Gulyas K, Bodnar N, Nagy Z, et al. Real-life experience with switching TNF- α inhibitors in ankylosing spondylitis. *Eur J Health Econ* 2014;15 Suppl 1:S93-100.
30. Ciurea A, Exer P, Weber U, et al. Does the reason for discontinuation of a first TNF inhibitor influence the effectiveness of a second TNF inhibitor in axial spondyloarthritis? Results from the Swiss Clinical Quality Management Cohort. *Arthritis Res Ther* 2016;18:71.

Table 1: Characteristics of patients who received a second TNFi, by type of switch (n=143)

		Change mAb–mAb, N=55	Change mAb–SR or SR–mAb, N=88
Women, n (%)		41 (74.5)	65 (73.9)
Age at initiation of 1st TNFi (years), mean (SD)		44.3 (13.2)	44.2 (10.91)
Age at initiation of 2 nd TNFi (years), mean (SD)		45.4 (13.1)	45.4 (10.92)
Age at SpA diagnosis, mean (SD)		42.8 (13.1)	42 (11.21)
Symptoms duration before initiation of the 1 st TNFi (months), means (SD)		55.8 (52.7)	44.7 (44.2)
Symptoms duration before initiation of the 2 nd TNFi (months), means (SD)		69.5 (54.4)	55.9 (44.0)
Center, n (%)	Orleans	18 (32.7)	27 (30.7)
	Tours	35 (63.6)	45 (51.1)
	Blois	2 (3.6)	16 (18.2)
SpA phenotype, n (%)	Axial radiographic	27 (49.1)	38 (41.2)
	Axial non-radiographic	7 (12.7)	13 (14.8)
	Erosive arthritis	0 (0)	6 (6.8)
	Non-erosive arthritis	4 (7.3)	5 (5.7)
	Enthesitic	1 (1.8)	2 (2.3)
	Mixed	16 (29.1)	24 (27.3)
HLAB27 positivity, n (%) (N=119)		16/43 (37.2)	38/76 (50.0)
ASAS classification criteria fulfilled, n (%)		43 (78.2)	69 (78.4)
mNY classification criteria fulfilled, n (%)		27 (49.1)	38 (43.2)
Reason for withdrawal of the 1st TNFi, n (%)	Primary failure	18 (32.7)	36 (40.9)
	Secondary failure	27 (49.1)	36 (40.9)
	Safety issue	9 (16.4)	16 (18.2)
	Remission	1 (1.8)	0
Current smoker at baseline, n (%) (N=74)	No	21/27 (77.8)	25/47 (53.2)
	Yes	6/27 (22.2)	22/47 (46.8)
NSAID intake at baseline, n (%)	No	26 (47.3)	34 (38.6)
	Yes	29 (52.7)	54 (61.4)
MTX intake at baseline, n (%)	No	44 (80)	72 (81.8)
	Yes	11 (20)	16 (18.2)
BASDAI at initiation of 1st TNFi, mean (SD)		5.9 (1.7)	6.4 (1.54)
BASDAI at initiation of 2 nd TNFi, mean (SD)		6.7 (1.3)	6.1 (1.41)
CRP level at initiation of 1st TNFi (mg/l), mean (SD)		5.6 (10.1)	6.6 (12.41)
CRP level at initiation of 2 nd TNFi (mg/l), mean (SD)		6.5 (11.2)	6.3 (12.03)
Duration of the 2 nd TNFi (months), mean (SD)		36.2 (32.9)	40.8 (35.8)

ASAS, Assessment of SpondyloArthritis Society; mNY, modified New York; HLAB27, human leukocyte antigen B27; NSAID, non-steroidal anti-inflammatory drug; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; mAb, monoclonal antibody.

Figure 1: Flow of patients with spondyloarthritis (SpA) in the study

TNFi, tumor necrosis factor inhibitor; mAb, monoclonal antibody, SR, soluble receptor.

Figure 2: Drug survival of the second TNFi by type of switch between the first and second TNFi (mAb–mAb in blue, mAb–SR or the reverse in red)

Figure 3: Drug survival of the second TNFi by type of switch between the first and second TNFi (mAb–mAb in blue or mAb–SR and the reverse in red) in patients who stopped the first TNFi because of lack of efficacy (N=137).

Figure 4: Drug survival of the second TNFi by reason for withdrawal of the first TNFi (primary failure in blue line, secondary failure in red line and side effect in green line).