Clinical and Experimental Rheumatology 2011; 29: 1010-1013.

Switching between tumour necrosis factor blockers in spondyloarthritis: a retrospective monocentre study of 222 patients

S. Dadoun, G. Geri, S. Paternotte, M. Dougados, L. Gossec

Paris Descartes University, Faculty of Medicine; APHP, Rheumatology B Department, Cochin Hospital, Paris, France.

Sabrina Dadoun, MD
Guillaume Geri, MD
Simon Paternotte, Statistician
Maxime Dougados, MD, PhD
Laure Gossec, MD, PhD

Please address correspondence to:
Dr Sabrina Dadoun,
Service de Rhumatologie B,
Hôpital Cochin,
27, rue du Faubourg Saint-Jacques,
75014 Paris, France.
E-mail: sabrinadadoun@gmail.com

Received on May 7, 2011; accepted in revised form on May 20, 2011.

Key words: spondyloarthritis, tumour necrosis factor blockers, switch, effectiveness, retention

Competing interests: none declared.

ABSTRACT

Objective. *To assess the frequency and effectiveness of switching TNF blockers in spondyloarthritis, and the predisposing factors of this effectiveness.*

Methods. *This was a retrospective systematic monocentre study; inclusion criteria were definite spondyloarthritis (Amor's criteria) and introduction of a first TNF blocker after January 2004. The retention rate of the first and second TNF blocker (if applicable) was evaluated (Kaplan-Meier technique). Patients' characteristics were compared with regard to requirement for switching. Predisposing factors of retention of the second TNF blocker were analysed (log-rank, Cox).*

Results. *A total of 222 patients started a first TNF blocker; 79% fulfilled the New York modified criteria, with increased CRP (75%) and median BASDAI of 50 (35-61). Mean follow up was 29±20 months (i.e. a total of 538 patient-years). By the end of follow-up, 72 patients (32%) had switched to a second TNF blocker. Patients who switched had more peripheral enthesitic symptoms (p=0.01) and a tendency for more peripheral involvement (p=0.06). Retention of the first and second TNF blocker was similar (p=0.32). No predictive factors were found for retention of the second TNF blocker; including no difference between TNF blockers and between reasons for stopping the first.*

Conclusion. *The effectiveness of switching TNF blocker in spondyloarthritis appears clinically relevant; no predictive factors of this effectiveness were evidenced.*

Introduction

Tumour necrosis factors blockers (TNF blocker) are extremely effective in spondyloarthritis (SpA). They have been used in clinical practice since 2000 after failing non-steroidal anti-inflammatory drugs (1). The efficacy of four TNF blockers (adalimumab, etanercept, infliximab and golimumab) has been demonstrated in short-term and in long-term studies (2-5). Few studies even reported a better retention rate of these drugs in SpA than in rheumatoid arthritis (6-7).

In some cases, the first TNF blocker is stopped because of inefficacy or intolerance. The usual practice in such a case is to switch to a second TNF blocker, in analogy to what is done in rheumatoid arthritis (8). However there are few data examining the efficacy of switching TNF blockers in SpA (9-14). Evaluating the second TNF blocker efficacy is a major issue because no other biologics are available today in active SpA and the retention rate of the drug is an interesting and validated method to assess this efficacy in real clinical practice (7). The objectives of the present study were to analyse, (a) the characteristics of SpA patients necessitating a TNF blocker switch, (b) the effectiveness of a second TNF blocker in SpA, (c) and to determine the predisposing factors of retention to the second TNF blocker.

Methods

Study design: retrospective study in a tertiary-referral centre.

Patient selection: computerised search in the unit database. Key words were: "spondylarthropathies" and "TNF blockers" for the period: January 2004 to October 2009. Patients were included if they had SpA according to Amor's criteria, they initiated their first TNF blocker between January 2004 and October 2009 and they were followed at least 3 months after TNF blocker initiation. All patients satisfying these criteria were analysed, whether they subsequently switched TNF blocker or not.

Patients characteristics: To compare patients who switched TNF blocker versus those who did not switch, characteristics were collected for each patient: demographic data (date of birth, sex, B27 status), symptom duration, disease characteristics (axial, peripheral and/or peripheral enthesitic symptoms, extra-articular manifestations), BASDAI, C-reactive protein (CRP) (assessed as elevated yes/no over entire follow-up) and satisfying the modified New York criteria.

Assessment of effectiveness of switching: Retention rate was defined as the percentage of patients still on treatment over time. At initiation of a TNF blocker, major disease characteristics justifying TNF blocker initiation were collect-

Table I. Characteristics of 222 patients initiating a first TNF blocker according to the need for a switch to a second TNF blocker or not.

	All patients	Patients not switching	Patients with 1 or more switches	*p*-value*
Number of patients	222	150	72	
Male sex, n (%)	156 (70.3)	110 (73.3)	446 (63.9)	0.16
Satisfying New York modified criteria**, n. (%)	175 (78.8)	123 (82.0)	52 (72.2)	0.11
HLAB27 positive antigen** n. (%)	156 (78.4)	105 (80.8)	51 (73.9)	0.28
At first TNF blocker introduction:				
- Median age (IQR), years	38.9 (31.2 ; 46.9)	39.3 (31.2; 47.6)	337.9 (31.4; 46.8)	0.52
- Median symptom duration (IQR), years**	12.1 (6.4 ; 21.6)	12.0 (7.1; 22.4)	12.5 (3.8; 19.8)	0.21
- Median BASDAI (IQR)	50.0 (35.0 ; 61.0)	47.0 (35.0; 60.0)	52.5 (35.5; 67.0)	0.25
- DMARD associated n. (%)	66 (30.1)	41 (27.3)	26 (36.1)	0.21
CRP elevation at any time point, n. (%)	165 (76.4)	110 (75.9)	55 (77.5)	0.87
SpA manifestations, n. (%)				
- Axial	218 (98.2)	147 (98.0)	71 (98.6)	1.00
- Peripheral joints	123 (55.7)	76 (51.0)	47 (65.3)	0.06
- Peripheral entheses	103 (46.6)	60 (40.3)	43 (59.7)	0.01
Associated manifestation at any time point, n. (%)				
- Uveitis	54 (24.3)	38 (25.3)	16 (22.2)	0.74
- Inflammatory bowel disease	25 (11.3)	14 (9.3)	11 (15.3)	0.26
- Psoriasis	39 (17.6)	27 (18.0)	12 (16.7)	0.85

*p-value comparing patients not switching and patients with one or more switches.
**% calculated on available data.

ed (axial, peripheral and/or peripheral enthesitic symptoms, extra-articular manifestation). At the stop of the TNF blocker, the reason for withdrawal was classified as follows: (a) primary inefficacy : no efficacy noted after the first three months of treatment (patient's and physician's opinion); (b) loss of efficacy (after at least 3 months of efficacy estimated by the patient or the physician); (c) adverse event; (d), and other (*e.g.* pregnancy, patients' wish).

Potential factors associated with the effectiveness of the first and the second TNF blocker: Factors potentially associated with the retention rate of the first and the second TNF blocker were analysed, including patients' and disease's characteristics (age, sex, B27 antigen, satisfying the modified New York criteria), disease's activity at TNF blocker initiation (CRP, association with a DMARD, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) level binarised by median) and major reason for prescription/interruption (primary inefficacy, loss of efficacy, adverse event, other).

Statistical analysis

Patients' characteristics were compared using non-parametric Wilcoxon/Fisher tests with a level of significance set at 5% bilaterally. For patients who switched, the second TNF blocker retention rate was assessed and compared to the first TNF blocker retention rate of the whole population using Kaplan-Meier survival curves and log rank analysis. In order to find potential factors associated with the effectiveness of the first and the second TNF blocker, a log rank analysis then Cox regression (when the *p*-value of the log rank analysis was <0.20) were applied. Analyses were performed using SAS 9.1.

Results

The computerised search selected 709 patients, of whom 46 (6.5%) did not have SpA, 226 (31.9%) did not initiate a first TNF blocker during the period of interest and 215 (30.3%) were only seen once in our department. Thus, 222 SpA patients started a first TNF blocker between 2004 and 2009 and were included in the analysis.

Patients' characteristics: Among the 222 patients, 175 (78.8%) satisfied the modified New York criteria and 206 (92.8%) satisfied the new ASAS criteria for axial spondylarthritis. Median age was 38.9 (interquartile range (IQR): 31.2-46.9) years, 156 (70.3%) were men and 156/199 (78.4% of available data) were positive for B27 antigen. Median symptom duration was 12.1 (IQR: 6.4-21.6) years (Table I). At first TNF blocker initiation, axial manifestation justifying TNF blocker prescription concerned 168 patients (75.7%), including 122 (81.3%) non switchers, and 46 (63.9%) switchers (p=0.007).

Follow-up: Mean follow-up of the 222 patients was 29.0 months (SD: 20.1), *i.e.* a total follow-up of 538 patient-years. The median follow-up was 22 months for the first TNF blocker and 17 months for the second. The first TNF blocker was etanercept (n=117, 52.7%), adalimumab (n=60, 27.0%) or Infliximab (n=45, 20.3%).

Frequency of switches: Among the 222 patients, 111 (50.0%) stopped the first TNF blocker over the duration of follow-up and 72 patients switched for a second TNF blocker. Reasons for stopping were primary inefficacy (27/111, 24.3%; 16/72, 22.2%), loss of efficacy (39/111, 35.2%; 30/72, 41.7%), adverse events (23/111, 20.7%; 14/72, 19.4%) or other causes (22/111, 19.8%; 12/72, 16.7%). The second TNF blocker was adalimumab (37/72, 51.4%), etanercept (23/72, 31.9%) or infliximab (12/72, 16.7%). At the end of follow-up, 35 of the 72 (48.6%) patients who had switched to a second TNF blocker, had stopped it. Reasons for stopping the second TNF blocker were primary inefficacy (16, 45.7%), loss of efficacy (7, 20.0%), adverse events (4, 11.4%) or other (8, 22.9%). In all, 21 (9.5%) patients switched twice.

Characteristics of "switchers": Patients who switched, compared to patients who did not, had more peripheral enthesitic involvement (59.7% *versus* 40.3% respectively, p=0.01) and a tendency for more peripheral involvement (65.3% *vs.* 51.0% respectively, p=0.06) (Table I). Reasons for stopping the first and second TNF blocker were compared: a significant difference for

primary inefficacy between the two groups was found (p=0.02) but no difference for loss of efficacy, adverse events or others. Among patients who stopped a TNF blocker, some patients did not start a new one (39 patients (35%) after the first TNF blocker, 14 patients (19.4%) after the second). Major reasons were related to intolerance (41.0% and 42.8%, respectively) or to inefficacy (38.5% and 35.7%, respectively).

Retention rate: Retention rate at one year was 65.0% for the first TNF blocker and 60.0% for the second (p=0.10). The survival curves of the first and the second TNF blocker did not differ significantly (p=0.32). (Fig. 1)

Factors associated with the effectiveness of the first TNF blocker: In the univariate analysis, male sex (p=0.03), B27 antigen positivity (p=0.01), satisfying the New York modified criteria (p=0.02), shorter symptom duration (p=0.03), an axial predominant disease (p=0.01) and elevated CRP (p=0.03) at baseline were associated with higher retention of the first TNF blocker. In the Cox model, only predominant axial manifestations were associated with the retention rate (hazard ratio = 0.44, 95% confidence interval 0.25–0.79).

Factors associated with the efficacy of the second TNF blocker: None of the factors analysed were associated with the retention rate of the second TNF blocker (Table II). In particular, neither the type of TNF blocker, nor the reason for stopping the first TNF blocker was found to be significant.

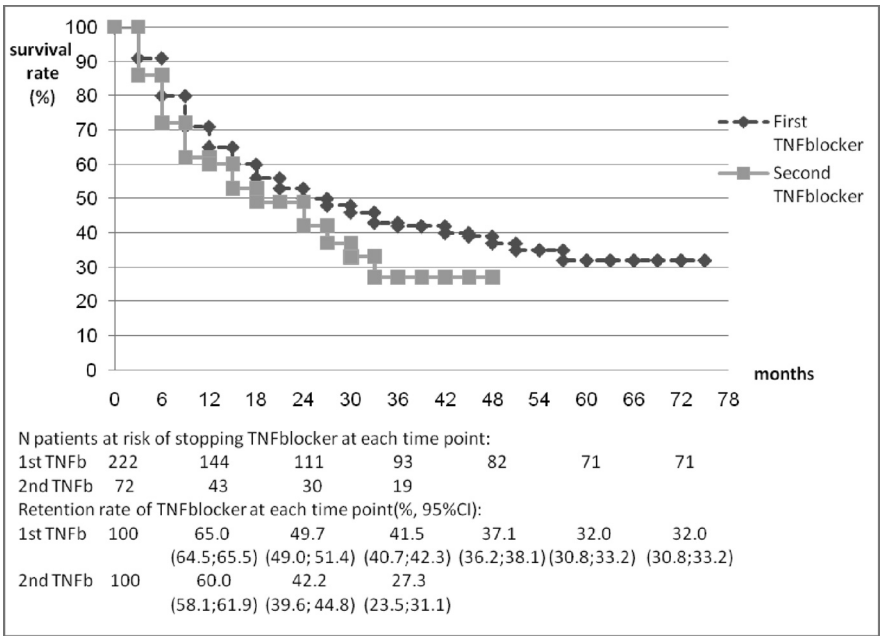

Fig. 1. Kaplan Meier survival curve comparing the first (black line) *vs*. the second (grey line) TNF blocker, in months. Median duration was 22 months and 17 months for first and second TNF blockers. For patients who stopped TNF blocker during the follow-up, median duration was 7.9 months and 5.6 months, respectively.

Table II. Potential predisposing factors explaining the retention rate of the second TNF blocker in 72 SpA patients.

	Log rank analysis		Cox model
	Hazard ratio (95% confidence interval)	p-value	Hazard ratio (95% confidence interval)
Type of TNF blocker	1.08 (0.67 ; 1.75)	0.08	1.21 (0.77 ; 1.90)
Age (binarised by median)	0.71 (0.33 ; 1.53)	0.38	---
Sex (male *vs*. female)	0.59 (0.27 ; 1,25)	0.17	1.46 (0.75 ; 2.83)
% HLA B27*	0.64 (0.28 ; 1.45)	0.28	---
% NY modified criteria	0.86 (0.39 ; 1.93)	0.72	---
Major manifestation* (axial *vs*. other)	1.35 (0.51 ; 3.54)	0.54	---
Association with DMARD (yes/no)	0.71 (0.28 ; 1.79)	0.47	---
Initial BASDAI* (binarised by median)	0.85 (0.21 ; 3.42)	0.82	---
CRP elevation* (yes/no)	0.50 (0.22 ; 1.19)	0.09	0.64 (0.28 ; 1.42)
Reason for stopping the first TNF blocker (inefficacy *vs*. intolerance)	1.54 (0.63 ; 3.74)	0.34	---

*Some data were not available: 64 patients were analysed for the presence of B27 antigen, 58 for major localisation, 35 for association with DMARD, 71 for CRP elevation, 34 for BASDAI.

Discussion

The present work reports the effectiveness of switching from a first to a second TNF blocker in SpA. In this study, the second TNF blocker was as effective as the first TNF blocker, as assessed through retention rates, highlighting the clinical relevance of switching. Furthermore no factors predicting the retention of the second TNF blocker could be evidenced, indicating that switching may be a relevant option for all patients, whatever the disease characteristics, the type of TNF blocker and the reason for stopping the first TNF blocker.

Some interesting points have to be noted. First, patients who switched had more peripheral enthesitic manifestations. TNF blockers may be less efficient in these patients (possibly, these patients with polyenthesopathy may have fibromyalgia-like syndromes). Second, the retention rate of the first TNF blocker was quite low in our study compared to previous publications (6). We previously reported rather low retention rates in our centre (7). Possible reasons include the selection of patients in this tertiary-care centre the long mean disease duration, the non-restrictiveness of the French legislation regarding therapeutic decisions and a rather low BASDAI score at initiation of the first TNF blocker. Furthermore, comparisons with other published studies are difficult, since the present population included patients with SpA, not with ankylosing spondylitis (AS) (9-14). However, it is noteworthy that the predisposing factors of retention of the first TNF blocker reported here are in

keeping with the published literature (15).

There are few studies reporting switches between TNF blockers in SpA but most of them with only few "switchers" (9-14). Two recent studies (one open label follow-up of an adalimumab trial, and the NORDMARD register) confirm the interest of switching, with however a higher efficacy for the first TNF blocker (13-14). This difference in effectiveness was not shown in our study, maybe because of a smaller sample size or because patients' characteristics were different (SpA *vs*. AS). However, an important number of switches was observed in our study and allowed relevant results. In conclusion, the present study confirms that switching TNF blockers is effective in SpA whatever the reason of withdrawal. More studies are needed to confirm these conclusions.

References

1. BRAUN J, DAVIS J, DOUGADOS M, SIEPER J, VAN DER LINDEN S, VAN DER HEIJDE D: 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.
2. BRAUN J, BRANDT J, LISTING J *et al*.: Two year maintenance of efficacy and safety of infliximab in the treatment of ankylosing spondylitis. *Ann Rheum Dis* 2005; 64: 229-34.
3. 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.
4. VAN DER HEIJDE D, SCHIFF MH, SIEPER J *et al*.: Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. *Ann Rheum Dis* 2009; 68: 922-9.
5. INMAN RD, DAVIS JC JR, 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.
6. CARMONA L, GOMEZ-REINO JJ: Survival of TNF antagonists in spondylarthritis is better than in rheumatoid arthritis. Data from the Spanish registry BIOBADASER. *Arthritis Res Ther* 2006; 8: R72.
7. DUCLOS M, GOSSEC L, RUYSSEN-WITRAND A *et al*.: Retention rates of tumor necrosis factor blockers in daily practice in 770 rheumatic patients. *J Rheumatol* 2006; 33: 2433-8.
8. LLOYD S, BUJKIEWICZ S, WAILOO AJ, SUTTON AJ, SCOTT D: The effectiveness of anti-TNF-{alpha} therapies when used sequentially in rheumatoid arthritis patients: a systematic review and meta-analysis. *Rheumatology* (Oxford) 2010; 49: 2313-21.
9. CANTINI F, NICCOLI L, BENUCCI M *et al*.: Switching from infliximab to once-weekly administration of 50 mg etanercept in resistant or intolerant patients with ankylosing spondylitis: results of a fifty-four-week study. *Arthritis Rheum* 2006; 55: 812-6.
10. CONTI F, CECCARELLI F, MAROCCHI E *et al*.: Switching tumour necrosis factor alpha antagonists in patients with ankylosing spondylitis and psoriatic arthritis: an observational study over a 5-year period. *Ann Rheum Dis* 2007; 66: 1393-7.
11. COATES LC, CAWKWELL LS, NG NW *et al*.: Real life experience confirms sustained response to long-term biologics and switching in ankylosing spondylitis. *Rheumatology* (Oxford) 2008; 47: 897-900.
12. PRADEEP DJ, KEAT AC, GAFFNEY K, BROOKSBY A, LEEDER J, HARRIS C: Switching anti-TNF therapy in ankylosing spondylitis. *Rheumatology* (Oxford) 2008; 47: 1726-7.
13. RUDWALEIT M, VAN DEN BOSCH F, KRON M, KARY S, KUPPER H: Effectiveness and safety of adalimumab in patients with ankylosing spondylitis or psoriatic arthritis and history of anti-tumor necrosis factor therapy. *Arthritis Res Ther* 2010; 12: R117.
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. LORD PA, FARRAGHER TM, LUNT M, WATSON KD, SYMMONS DP, HYRICH KL: Predictors of response to anti-TNF therapy in ankylosing spondylitis: results from the British Society for Rheumatology Biologics Register. *Rheumatology* (Oxford) 2010; 49: 563-70.