Psoriatic arthritis treated by anti-TNFs: a monocentric trial of 102 cases in Auvergne, France

M. Soubrier[1], B. Pereira[2], T. Frayssac[1], D. Abdi[1], M. Couderc[1], C. Daron[1], S. Malochet-Guinamand[1], S. Mathieu[1], Z. Tatar[1], A. Tournadre[1], J.-J. Dubost[1]

[1]Department of Rheumatology, [2]Biostatistics and Research Department (DRCI), CHU Hôpital Gabriel Montpied, Clermont-Ferrand, France.

Abstract

Objective

While several registries have already evaluated the retention of anti-TNF therapy in psoriatic arthritis (PsA), they sometimes reach divergent conclusions. Our study therefore sought to assess therapeutic retention rates and predictive factors of response in a patient cohort from Auvergne, France, followed up in routine clinical practice.

Methods

Medical records of all PsA patients treated from 2002 to May 2015 were analysed. PsA diagnosis was established based on the CASPAR criteria.

Results

In total, 102 patients were analysed, comprising 62 men (44.6±12.6 years) and 40 women (37.8±13.4). Mean PsA evolution was 2.7 years (0.8–11.2). The most common forms were peripheral (47/102, 45.1%) and mixed (46/102, 46.1%) PsA. The anti-TNF treatment initiated was etanercept in 47 cases (45.2%), adalimumab in 29 (27.9%), infliximab in 20 (19.2%), and golimumab in six [5.8%]. In 28 cases (27.4%), anti-TNF was associated with methotrexate (MTX). Overall, the median duration of anti-TNF retention was 76.5 months. The hazard ratios (HR) for treatment cessation did not significantly differ between the etanercept and monoclonal antibody groups (HR=1.35[0.96–1.93], p=0.08). After 5 years, approximately 30.8% of etanercept patients and 68.8% of monoclonal antibody patients (adalimumab 71.2%; infliximab 67.2%) were still being treated. Combining with MTX did not prolong the overall retention rate (HR=0.85[0.37–1.96], p=0.71). Tobacco use was predictive of discontinuation (p=0.03).

Conclusion

Our study demonstrates good anti-TNF treatment retention in PsA patients, as well as confirming the deleterious effect of smoking while providing no argument in favour of combined treatment with MTX to improve maintenance

Key words

psoriatic arthritis, tumour necrosis factor receptors/therapeutic use, treatment outcome.

Martin Soubrier, MD, PhD
Bruno Pereira, PhD
Thomas Frayssac, MSc
Dihya Abdi, BSc
Marion Couderc, MD
Coline Daron, MD
Sandrine Malochet-Guinamand, MD
Sylvain Mathieu, MD
Zuzana Tatar, MD
Anne Tournadre, MD
Jean-Jacques Dubost, MD

Please address correspondence to:
Martin Soubrier,
Rheumatology, DRCI,
C.H.U. Hôpital Gabriel Montpied,
63003 Clermont-Ferrand Cedex 1, France.
E-mail: msoubrier@chu-clermontferrand.fr

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Introduction

Anti-tumour necrosis factor (TNF) agents have greatly improved care for psoriatic arthritis (PsA) patients. These drugs are indicated when disease-modifying treatments fail in peripheral PsA or non-steroidal anti-inflammatory drugs (NSAIDs) fail in axial PsA (1-5). The efficacy of the anti-TNF drugs infliximab, adalimumab, certolizumab pegol, golimumab, and etanercept has been widely demonstrated in randomised trials compared to placebo (6-11). Medical registries enable us to better assess anti-TNF drugs in routine practice, providing the data needed to confirm their efficacy, demonstrate the usefulness of anti-TNF drug rotation if primary or secondary treatments fail, and assess retention rates (12-16). They have also helped us find predictive factors of response, non-response, and therapeutic retention. Older age, female gender, associated corticosteroid treatment, and tobacco use are known to be potential predictive factors of non-response (12, 17). While apparently not improving response rate, co-prescription with methotrexate (MTX) can exhibit favourable effects on the retention of anti-TNF treatment, which is also the case for elevated C-reactive protein levels (13; 18). Our study therefore sought to assess therapeutic retention rates and predictive factors of response in a patient cohort receiving these treatments in Auvergne, France, followed up in routine clinical practice.

Materials and methods

Medical records of all PsA patients treated from 2002 to May 2015 were analysed. PsA diagnosis was established based on the classification of psoriatic arthritis (CASPAR) criteria, thus allowing for including peripheral, axial, and mixed forms (19).

We collected demographic characteristics and patient medical histories, as well as data on disease-modifying treatments, corticosteroid therapy, and NSAID treatments. We recorded the following data both on initiating anti-TNF treatment and at the 6-month follow-up: number of night-time awakenings; duration of morning joint loosening-up; PsA-related pain and activity (Visual Analogue Scale [VAS] 0–10), if peripheral, and number of painful or swollen joints if axial; Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); Bath Ankylosing Spondylitis Functional Index (BASFI). Response was defined according to the European League Against Rheumatism (EULAR) criteria, if peripheral effects predominated, and on BASDAI improvement if axial effects predominated. Treatment discontinuation was considered definitive either when noted as such by the rheumatologist managing the patient, when no treatment renewal was noted, or when another treatment was initiated. Reasons for discontinuation were categorised as inefficacy (rheumatologist's assessment), adverse effects, or other, comprising reasons such as pregnancy, surgery, drop-out, and remission. Inefficacy was defined as the primary reason when treatment was stopped at 6 months. When there were several reasons for treatment discontinuation, all were taken into account. Predictive factors of response and therapeutic retention were investigated. We analysed only the survival curves for the three most-prescribed anti-TNF drugs. Several patients already had a serum bank set up as part of a study on atheroma and spondyloarthritis (IRB: 00008526 of CPP, No. AU630) and were able to benefit from the anti-TNF agent and anti-TNF antibody assay using the Theradiag diagnostic kit.

Statistical analysis

Statistical analysis was performed using Stata software, v. 12 (StataCorp, College Station, TX, USA). The tests were two-sided, with a Type I error set at α=0.05. Baseline characteristics were presented as mean ± standard deviation (SD) or median (interquartile range) for continuous data (assumption of normality assessed using the Shapiro-Wilk test), and as the number of patients and associated percentages for categorical parameters. Comparisons of patient characteristics between groups were made using the chi-squared or Fisher's exact tests for categorical variables, and analysis of variance (ANOVA) or the Kruskal-Wallis test for quantitative parameters (homoscedasticity verified

Table I.

	Total (n=102)	Infliximab (n=20)	Etanercept (n=47)	Adalimumab (n=29)	*p*
Demographic characteristics					
Age at diagnosis, mean ± SD	41.9 ± 13.3	40.7 ± 10.0	45.6 ± 14.6	37.3 ± 12.7	0.04
Duration of evolution	7.4 ± 9.0	8.3 ± 8.6	6.9 ± 9.1	7.5 ± 9.6	0.63
Women, n (%)	40 (39.2)	8 (40.0)	18 (38.3)	10 (34.5)	0.91
Number of previous DMARDs	1.45 ± 0.79	1.70 ± 0.98	1.64 ± 0.90	1.41 ± 0.78	0.50
Corticotherapy	36 (35.3)	5 (25.0)	22 (46.8)	8 (27.6)	0.12
CV FHx (MI, stroke)	4 (3.9)	0 (0.0)	2 (4.3)	2 (6.9)	0.67
Current smokers, n (%)	33 (32.4)	5 (25.0)	16 (34.0)	9 (31.0)	0.76
Hypertension, n (%)	25 (24.5)	5 (25.0)	15 (31.9)	5 (17.2)	0.36
BMI, mean ± SD	28.7 ± 6.1	31.4 ± 8.0	28.3 ± 5.7	27.5 ± 4.4	0.32
Diabetes, n (%)	10 (9.8)	4 (20.0)	4 (8.5)	2 (6.9)	0.31
Dyslipidaemia (treated), n (%)	12 (11.8)	3 (15.0)	5 (10.6)	4 (13.8)	0.78
Osteoporosis, n (%)	10 (9.8)	2 (10.0)	5 (10.6)	2 (6.9)	0.90
Characteristics of the illness					
Form, n (%)					
Axial	9 (8.8)	1 (5.0)	3 (6.4)	5 (17.2)	0.52
Peripheral	46 (45.1)	8 (40.0)	22 (46.8)	13 (44.8)	
Peripheral + axial	47 (46.1)	11 (55.0)	22 (46.8)	11 (37.9)	
DAS28 ESR, mean ± SD	4.1 ± 1.2	4.28 ± 1.25	4.19 ± 1.23	4.01 ± 1.14	0.81
DAS28 CRP, mean ± SD	4.1 ± 1.0	4.46 ± 0.83	4.11 ± 1.20	3.96 ± 0.79	0.22
BASDAI, mean ± SD	50.2 ± 24.5	58.23 ± 16.61	47.30 ± 25.89	46.18 ± 27.31	0.24
CRP, median [IQR]	10.8 [4.2–31.1]	23.0 [10–40.8]	13.2 [4.6–44.8]	5.6 [2.8–16.4]	0.02

SD: standard deviation; DMARD: disease-modifying anti-rheumatic drug; CV FHx: cardiovascular family history; MI: myocardial infarction; BMI: body mass index; DAS28: Disease Activity Score 28; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; IQR: interquartile range.

by the Bartlett test). Censored data was determined using the Kaplan-Meier method. Log-rank statistic was used in univariate analysis to assess the prognostic value of patient characteristics. A Cox proportional-hazards regression was then applied to evaluate prognostic factors in multivariate analysis, according to univariate results and the following clinically-relevant parameters (15): age, gender, and number of disease-modifying anti-rheumatic drugs (DMARD) and corticosteroid treatments. The proportional-hazard hypothesis was verified using the Schoenfeld test and plotting residuals. Interactions between potential predictive factors were also investigated. Results were expressed as hazard ratios (HR) with 95% confidence intervals (CI).

Results

In total, 102 patients were analysed, comprising 62 men (mean age: 44.6±12.6 years) and 40 women (37.8±13.4 years). The mean PsA evolution was 2.7 years (0.8–11.2). The most common PsA forms were peripheral (47/102, 45.1%) and mixed (46/102, 46.1%).

Mean Disease Activity Score 28 (DAS28) erythrocyte sedimentation rate (ESR) was 4.1±1.2, median DAS28 C-reactive protein (CRP) was 4.1±1.0, and mean BASDAI was 50.2±24.5. Mean CRP was 10.8 mg/L (4.2–31.1), yet 29.2% of patients exhibited no inflammatory syndromes (CRP <5 mg/L). Moreover, 19 (17%) were human leukocyte antigen (HLA) B27 carriers. Mean body mass index (BMI) was 28.7±6.1; 34.2% were obese (BMI >30) and 35.7% overweight (25 <BMI <30); 10 (9%) were diabetic, 11 (10%) were current smokers, and 22 (20%) former smokers.

Of the 102 patients, 96 had received disease-modifying treatments, predominantly MTX (80 [76.9%]), then sulfasalazine (38 [36.5%]) then leflunomide (12 [11.5%]), in order of frequency; 36 patients (35%) had received corticosteroid therapy, which was continued during anti-TNF treatment in 32 (88.9%) at a dose of 6.3 mg (1.5–13).

The anti-TNF treatment was etanercept in 47 cases (45.2%), predominantly alone (38 [80.9%]), or combined with MTX in nine (19.1%). The other anti-TNF treatments administered were adalimumab for 29 (27.9%), as monotherapy in 20 (69.0%) and combined with MTX in nine (31.0%), infliximab in 20 (19.2%), as monotherapy (16 [80%]) or combined with MTX (four [20%]), and golimumab in six [5.8%] all combined with MTX.

The patients' characteristics did not differ according to initiation of anti-TNF treatment except for age (p=0.04) and CRP level (p=0.02).

Response

Response was assessed at 6 months: 14% of patients were EULAR non-responders, 19.2% demonstrated moderate EULAR response, and 66.6% good EULAR response. Two-thirds of patients with isolated axial PsA exhibited 50% BASDAI improvement. Similar proportions of good or moderate response were observed in all anti-TNF groups: (infliximab: 55%; adalimumab: 48.3; etanercept 55.3%; p=0.82). Patient characteristics (age, gender, BMI, tobacco use, disease activity score, and associated disease-modifying treatment or corticosteroid therapy) did not differ between responders and non-responders in the peripheral or mixed PsA patients, except for higher CRP levels observed in responder patients (17.4 [5.6–45.0] *vs*. 8.9 [2.9–17.2]) (Table II).

Table II. Predictive factors of response in patients with peripheral or mixed PsA.

	No EULAR response	Good or moderate EULAR response	*p*
Age at diagnosis, mean±SD	43.5 ± 13.6	40.7 ± 13.5	0.32
Women, (%)	37.8%	37.3%	0.96
Duration of evolution, years mean ± SD	6.3 ± 8.6	8.4 ± 9.4	0.14
BMI, meanSD	30.1 ± 6.4	28.2 ± 5.9	0.27
Current smokers, (%)	31.1%	31.4%	0.98
Number of previous DMARDs	1.33 ± 0.77	1.57 ± 0.83	0.15
Corticosteroid therapy (%)	35.6%	38.0%	0.81
ESR, meanSD	20.9 ± 22.4	30.5 ± 26.9	0.08
CRP, median [IQR]	8.9 [2.9 – 17.2]	17.4 [5.6 – 45.0]	0.01

EULAR: European League Against Rheumatism; SD: standard deviation; DMARD: disease-modifying anti-rheumatic drug; BMI: body mass index; DAS28; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; IQR: interquartile range.

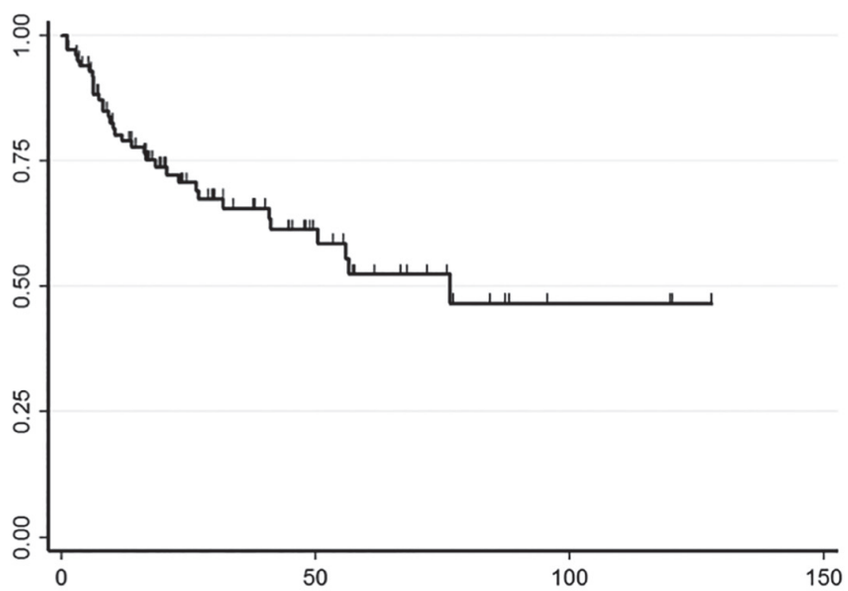

Fig. 1. Time to treatment discontinuation.

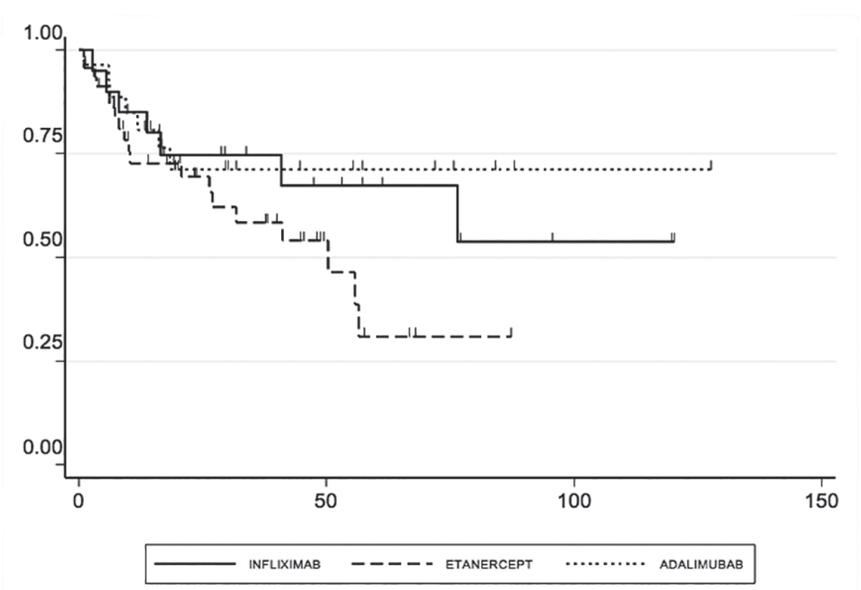

Fig. 2. Time to treatment discontinuation according to anti-TNF drug.

Retention rate of first anti-TNF treatment

A total of 35 (34.3%) had their treatment discontinued: 29 for inefficacy and the other six due to gastric adenocarcinoma, interstitial pulmonary syndrome, worsening chronic obstructive bronchopneumopathy, psoriasis, one occurrence of plantar fibromatosis, and one attempted suicide by self-immolation.

Overall, the median duration of anti-TNF retention was 76.5 months. The hazard ratios (HR) for treatment cessation did not significantly differ between the soluble receptor and monoclonal antibody groups (HR=1.35 [0.96–1.93], p=0.08) (Figs. 1-2). After 5 years, approximately 30.8% of the etanercept patients and 68.8% of monoclonal antibody patients (adalimumab 71.2%; infliximab 67.2%) were still receiving their respective treatments.

Combining with MTX did not prolong the overall retention rate (HR=0.85 [0.37–1.96], p=0.71). Analysis according to anti-TNF drug revealed no difference in favour of either etanercept (HR=1.23 [0.41–3.71], p=0.72) or monoclonal antibodies (HR=0.69 [0.19–2.45], p=0.57).

Predictive factors of treatment discontinuation

Based on previous findings in the literature, we assessed age, gender, concomitant inflammatory syndrome, weight, BMI, current smoking status, and initial corticosteroid therapy as predictive factors of treatment discontinuation. Only tobacco use turned out to be predictive of discontinuation (p=0.03).

Retention rate of second anti-TNF drug

In total, 34 patients received a second anti-TNF drug, which was maintained in 25 and discontinued in the remaining nine after an average of 7.7 months.

Assay of anti-TNF drugs and anti-TNF antibodies

Monoclonal antibodies. Of the 14 patients treated with infliximab, three were started on a different treatment due to inefficacy. In these three cases, infliximab could not be assayed while high levels of anti-infliximab antibod-

ies were present (>250 IU). Two of the 12 patients treated with adalimumab also had their treatment changed, with adalimumab unassayable in one, who exhibited anti-adalimumab antibodies, and the other patient exhibiting normal values, with no antibodies, despite the treatment having been changed due to inefficacy. In the other patients, the adalimumab assay revealed a value of 12 mg/L.

Soluble receptor. Etanercept was assayed in 22 patients, seven of whom were started on a different treatment due to inefficacy, with one exhibiting anti-etanercept antibodies and low serum levels. However, the etanercept assay (4.5±2.4mg/L *vs*. 4.1±0.5mg/L, p=0.26) revealed no difference between patients whose treatment was changed and those not.

Discussion

In our observational study, 85.8% of patients were responders according to the EULAR criteria. Our results were similar to those published by other studies applying the EULAR response criteria. In the IMPACT study, for example, which assessed the efficacy of infliximab on PsA and skin psoriasis, 89% of patients were EULAR responders at 16 weeks (21). In the RESPONSE study evaluating the effect of infliximab combined with MTX compared to MTX alone, 98% of the combination patients were EULAR responders *vs*. 72.9% of those receiving MXT alone (22). In the GO-REVEAL study, 64% of the patients receiving 50mg of golimumab were responders at 24 weeks, as were 78% of those receiving 100 mg, in comparison with 24% of the patients receiving the placebo (23). The EULAR responses were higher in our series than those of other registers. Good and moderate EULAR responses were observed, respectively, in 54% and 27% in the DANBIO registry, in 55% and 20% in the SSTAG register, and in 38% each in the BSRBR registry (12-14).

The median retention rate of the first anti-TNF treatment in our study was higher than those previously published. At 6.4 years, it was much higher than that reported in the DANBIO registry or the recently-published Lille series, where the median retention time was 2 years (14-24). In our study, despite there being no significant difference between the different treatment groups, etanercept was associated with the worst therapeutic retention. We reported 5-year retention rates of 30.8%, 67.2%, and 71.2% for etanercept, infliximab, and adalimumab, respectively, in contrast to the results of a previous single-centre study involving 65 patients, reporting corresponding rates of 76%, 56.7%, and 50% (25). However, in the British registry for psoriasis, etanercept was recorded to produce the worst retention compared to infliximab and adalimumab (26).

Although MTX did not enhance the efficacy of the anti-TNF drug in PsA, either in randomised trials or observational studies, some have suggested that it could increase the retention time of anti-TNF treatment (26). In the Norwegian Anti-Rheumatic Drug (NOR-DMARD) register, combination with MTX prolonged survival under anti-TNF treatment (p=0.07), markedly so for infliximab (p=0.01) and in a more moderate capacity for adalimumab (p=0.12). With etanercept, however, no benefit was observed (p=0.79) (18). Treatment discontinuation was most often secondary to adverse effects, and the authors suggested that MTX could prevent the formation of anti-drug antibodies (18). In the Swedish registry, MTX was also associated with a longer retention time (odds ratio [OR]: 0.64 [95% CI: 0.39–0.95]) due to fewer adverse effects (HR: 0.24 [0.11–0.52]) (13). In the Danish registry, absence of MTX was also associated with more treatment discontinuations (HR: 1.37 [1.07–1.75]), once again due to intolerance rather than treatment inefficacy (15). Conversely, in both the Canadian registry and our study, the presence of MTX did not affect anti-TNF treatment survival (28).

In our study, tobacco use was the only predictive factorof anti-TNF treatment discontinuation. The role of smoking had already been analysed in the DANBIO registry (17). Responses to anti-TNF treatment were weaker at 6 months in smokers (good EULAR response rates in 23% *vs*. 34%), who also exhibited weaker treatment adherence (1.56 [0.97–2.15] years *vs*. 2.43 [1.88–2.97] years). This was observed primarily in the infliximab (HR: 1.62 [1.06–2.48]) and etanercept (HR: 1.74 [1.14–2.66]) patients, though not for adalimumab (HR: 0.80 [0.52–1.23]). Smoking at baseline was also identified as an independent predictive factor of drug discontinuation in the NOR-DMARD register (HR: 1.52 [1.08–1.13]) (16). It was also a predictive factor of discontinuation in the British registry of psoriasis in terms of anti-TNF-treated patients (26).

Though only a small number of anti-TNF drug assays were performed in our study, we found no difference in etanercept concentrations between patients whose treatment had been changed due to inefficacy and those not. In rheumatoid polyarthritis, lower etanercept concentrations were documented in non-responders than responders (29). In addition, the etanercept levels were higher in both groups than the minimum efficacious dose reported by Daien (3.1 mg/L) (30). The adalimumab levels observed in our good-responder patients were well over the optimal values reported for managing either psoriasis (3.51–7.00 mg/L) or rheumatoid arthritis (5–8 mg/mL) (31; 32). Lastly, four patients whose treatment had been changed exhibited anti-drug antibodies, thereby justifying the therapeutic decision taken.

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