

CONCISE REPORT

Switching tumour necrosis factor α antagonists in patients with ankylosing spondylitis and psoriatic arthritis: an observational study over a 5-year period

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Objective: To evaluate the clinical response after switching from one tumour necrosis factor (TNF) α antagonist to another in patients with ankylosing spondylitis (AS) and psoriatic arthritis (PsA).

Methods: In this ongoing, longitudinal, observational study, data were prospectively collected on efficacy and safety since 2000 for patients starting biological treatments. The present analysis was restricted to patients with a diagnosis of spondyloarthritis (SpA) who switched from one TNF α antagonist to another because of inadequate efficacy or adverse events.

Results: In total, 589 anti-TNF α -naive patients were registered, of whom 165 had a diagnosis of SpA; 7 patients with AS and 15 with PsA received >1 TNF α antagonist. Two patients with PsA were treated with all the drugs. In all, 16 subjects switched from infliximab to etanercept, 7 from etanercept to adalimumab and 1 from etanercept to infliximab. Overall, a clinical response was seen in 75% of patients who changed from infliximab to etanercept, and in 57.1% who switched from etanercept to adalimumab.

Conclusions: The findings of this study on a selected population of patients with SpA indicate that the failure of an initial TNF α antagonist does not preclude the response to another one. Further trials are needed to confirm this preliminary observation.

The tumour necrosis factor (TNF) α antagonists infliximab, etanercept and adalimumab have been shown to be effective in controlling symptoms in ankylosing spondylitis (AS) and psoriatic arthritis (PsA), and in retarding radiological progression in PsA. These drugs are currently reserved for patients who are non-responsive to conventional treatments. Although there have been no direct comparison studies, the various TNF α antagonists appear to have similar efficacy, with a clinical response in 50–60% of patients. However, around 30% of patients with AS or PsA treated with these drugs withdraw from treatment due to adverse events (AEs) or loss of efficacy.¹ Data from clinical trials or national registers suggest that patients with rheumatoid arthritis (RA) who do not tolerate or do not respond to a TNF α antagonist may be successfully treated with another.^{2–5} To date, there have been few data on spondyloarthritis (SpA). Delaunay *et al* reported a favourable clinical outcome in 15 patients with SpA who switched from infliximab to etanercept because of inefficacy or intolerance.⁶ An open-label, prospective study has recently demonstrated the efficacy and tolerability of etanercept in 23 patients with active AS who were resistant or intolerant to infliximab.⁷

In this paper, we report the results of an ongoing, longitudinal, observational study, and evaluate the clinical response after switching from one TNF α antagonist to another in patients with AS and PsA within a 'real-life' clinical setting.

PATIENTS AND METHODS

In this ongoing, longitudinal, observational study, we prospectively collected data since 2000 on efficacy and safety for patients starting biological treatments in our rheumatology division.

The present analysis was restricted to patients with a diagnosis of SpA who switched from one TNF α antagonist to another, with a minimum of 6 months' follow-up by the end of December 2006 (the first SpA patient started treatment in December 2001). Patients with AS were classified according to the modified New York Criteria,⁸ and patients with PsA according to the Moll and Wright criteria modified by Helliwell.⁹ The choice of biological agent was based on clinical considerations only; thus, these patients represented a 'real-life' sample of subjects treated with TNF α antagonists. Infliximab 3–5 mg/kg was administered intravenously at weeks 0, 2 and 6, then every 6–8 weeks; etanercept (25 mg twice weekly) and adalimumab (40 mg alternate weekly) were given subcutaneously.

Clinical assessment

Patients were evaluated by the same rheumatologist at baseline (before starting the TNF α antagonist), every 3 months and at the last administration of the drug. Data, including demographics, diagnosis, date of diagnosis, comorbidities, past and present treatments, TNF α antagonist prescribed and date of beginning, concomitant medications, were recorded on a standardised form. Current disease activity in patients with AS was measured by the modified Ritchie Index,¹⁰ and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).¹¹ Clinical assessment in patients with PsA was performed according to the Psoriatic Arthritis Response Criteria (PsARC).¹² Each patient completed the Health Assessment Questionnaire (HAQ). Patient and physician global assessments (on a visual analogue scale, VAS) were also performed.¹³ Response to TNF α antagonist was defined by a 50% response on the BASDAI (BASDAI 50)¹⁴ for patients with AS, and by PsARC for patients with PsA. Drug discontinuation was based on the rheumatologist's opinion and the reason of withdrawal recorded as lack of efficacy (patients who never reached a satisfactory response), loss of efficacy (patients who relapsed

Abbreviations: AE, adverse events; AS, ankylosing spondylitis; ASAS, ASsessment in Ankylosing Spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; HAQ, Health Assessment Questionnaire; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Criteria; RA, rheumatoid arthritis; SpA, spondyloarthritis; TNF, tumour necrosis factor; VAS, visual analogue scale

Table 1 Clinical and therapeutic features of the patients

Pt	Diag	Sex	Disease duration (months)	Infliximab			Etanercept			Adimumab		
				Concomitant DMARD treatment	Treatment duration (months)	Reason for discontinuation	Concomitant DMARD treatment	Treatment duration (months)	Reason for discontinuation	Concomitant DMARD treatment	Treatment duration (months)	Reason for discontinuation
1	AS	F	48	MTX	12	IRR	MTX	21	Yes	—	—	—
2	AS	F	300	—	7	IRR	—	31	Yes	—	—	—
3	AS	F	288	—	20	IRR	—	18	Yes	—	—	—
4	AS	M	132	—	11	LoE	—	32	Yes	—	—	—
5	AS	F	144	—	24	LoE	SSZ	11	Yes	—	—	—
6	AS	M	60	SSZ	12	LoE	SSZ	3	No	LoE	—	—
7	PsA	F	96	MTX	5	IRR	LFN	33	Yes	—	—	—
8	PsA	F	192	—	3	IRR	—	36	Yes	—	—	—
9	PsA	M	60	MTX	12	LoE	—	32	Yes	—	—	—
10	PsA	M	84	Cs	36	LoE	—	12	Yes	—	—	—
11	PsA	F	372	MTX	27	LoE	—	24	Yes	—	—	—
12	PsA	M	72	—	25	LoE	—	18	Yes	—	—	—
13	PsA	F	72	MTX	10	AE*	—	24	Yes	—	—	—
14	PsA	F	228	MTX	7	Other†	—	6	Yes	—	—	—
15	PsA	M	72	MTX	6	IRR	Cs	12	No	LoE	LoE	LoE
16	PsA	F	336	—	8	LoE	—	3	No	LoE	—	LoE
17	PsA	F	60	—	—	—	—	3	—	IRR	—	—
18	PsA	F	60	—	—	—	MTX	12	—	LoE	LoE	LoE
19	PsA	F	60	—	—	—	MTX	6	—	LoE	LoE	—
20	PsA	F	24	—	—	—	MTX	12	—	LoE	LoE	—
21	PsA	F	65	—	—	—	—	3	—	AE‡	—	—
				Etanercept			Infliximab					
22	AS	M	36	—	6	LoE	MTX	16	Yes	—	—	—

Concom, concomitant; Cs, ciclosporin A; Diag, diagnosis; Discon, discontinuation; IRR, infusion/injection related reaction; LoE, lack of efficacy; LFN, leflunomide; LoE, loss of efficacy; MTX, methotrexate; SSZ, salazopyrine. *Autoimmune hepatitis; †surgery for hip replacement; ‡hypertransaminasaemia.

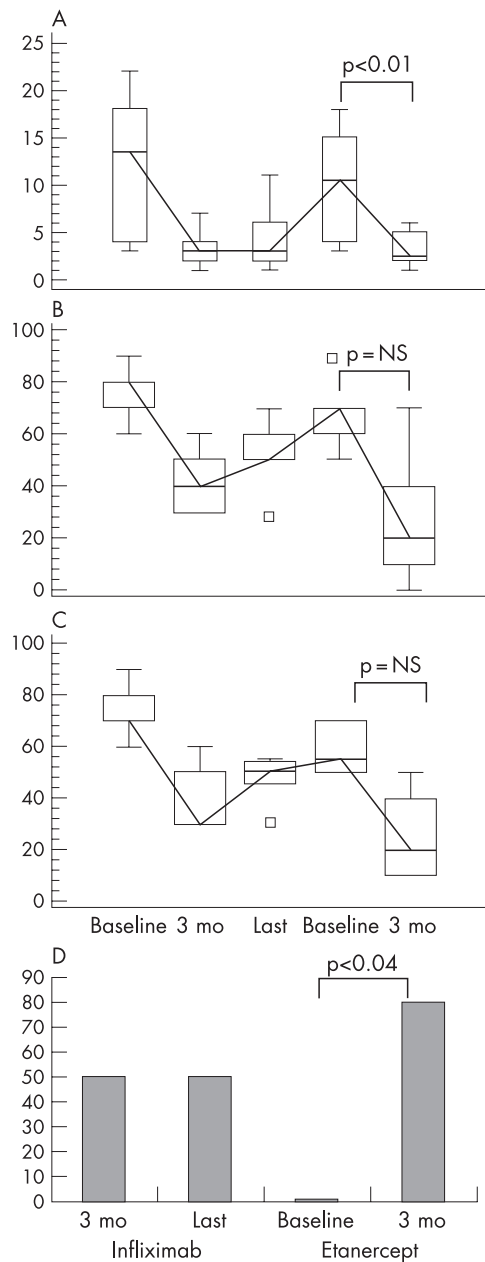


Figure 1 Clinical parameters in patients with AS ($n=6$) who switched from infliximab to etanercept. Box and whiskers plot (median, quartiles, range and possible extreme values) of (A) Ritchie Index, (B) patient and (C) physician global assessment (on visual analogue scale); (D) percentage of patients who had 50% improvement on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI 50). Values shown are the mean values at baseline (before infliximab treatment), after 3 months of infliximab treatment, at last visit while on infliximab, at baseline (before etanercept treatment) and after 3 months of etanercept treatment.

after an initial good response), AEs or other. The wash-out period between TNF α antagonists was 6 weeks.

Statistical analysis

Qualitative differences between subgroups were analysed by the χ^2 and Fisher exact tests. The Wilcoxon paired test was used to compare quantitative variables in the same group. Statistical significance was set at $p<0.05$.

RESULTS

The study comprised 589 anti-TNF α -naive patients, of whom 165 had a diagnosis of SpA. In total, 22 patients with SpA (7

patients with AS (mean age 33.5 years, range 22–49 years), and 15 with PsA (mean age 47.9 years, range 24–57 years)) received >1 TNF α antagonist (table 1). Two patients with PsA were consecutively treated with all three TNF α antagonists.

A clinical response was seen in 12/16 (75%) patients who changed from infliximab to etanercept, and in 4/7 (57.1%) who switched from etanercept to adalimumab (figs 1 and 2). Patients who switched because of AEs and those who changed because of inadequate efficacy (ie patients who never reached a satisfactory response, or patients who relapsed after an initial good response) presented a similar clinical response (70% and 61.5%, respectively). The mean duration of etanercept treatment was longer than the previous infliximab treatment (19.7 vs 14.1 months, respectively; NS). The mean duration of treatment was not different in patients treated with adalimumab after etanercept (7.3 vs 8.1 months, respectively; NS) (table 1).

Six patients with AS switched from infliximab to etanercept (mean age 31.8 years, range 16–49) (table 1). After 3 months of etanercept, the proportion of responders grew from 0% (baseline before etanercept) to 83.3% ($p<0.04$). Changes in Ritchie Index, patient and physician global assessment, and BASDAI 50 are shown in fig 1.

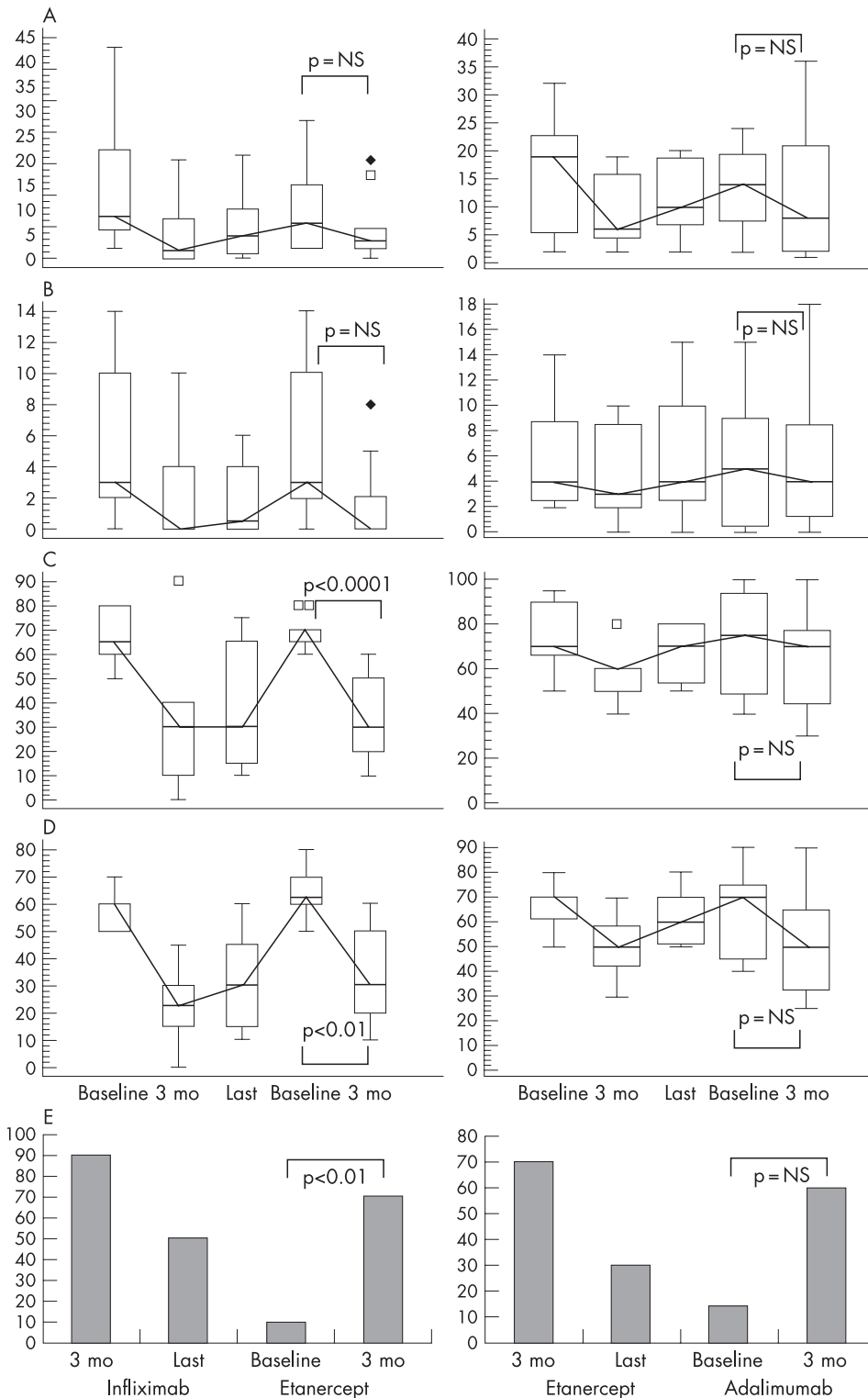
Ten patients with PsA switched from infliximab to etanercept (mean age 47 years, range 24–56). After 3 months of etanercept, the proportion of PsARC responders increased from 10% (baseline before etanercept) to 70% (fig 2), and HAQ score decreased significantly ($p<0.01$). Seven patients with PsA switched from etanercept to adalimumab (mean age 49.8 years, range 39–57). After 3 months of adalimumab, the proportion of PsARC responders increased from 14.3% (baseline before adalimumab) to 57.1% (fig 2).

One patient with AS received etanercept as first TNF α antagonist (table 1). He had a satisfactory response at 3 months, which was subsequently lost, thus he was switched to infliximab. After 3 months, a clinical response was seen.

DISCUSSION

The findings of this longitudinal, observational study on a selected population of patients with SpA indicate that the failure of a first anti-TNF α agent does not preclude the response to another, irrespective of the reason for switching.

The introduction of biological agents has allowed a radical change in the standard of treatment in SpA. Clinical response rates to anti-TNF α agents range from 43% to 71% by BASDAI 50 in patients with AS and from 62% to 87% by PsARC in subjects with PsA.¹ However, a significant proportion of patients withdraw from treatment because of failure or poor tolerability. Because the TNF α antagonists differ in chemical structure, mechanism of action and safety profile, there is a strong rationale for switching. Several reports support this possibility and, switching to another TNF α antagonist has now become a common practice in RA.^{2–5} Very few data are currently available for patients with SpA. Delaunay *et al*, in their retrospective evaluation, described 15 patients with various SpAs who switched from infliximab to etanercept because of AEs or inadequate efficacy. A clinical response was observed in 42.8% of the seven patients with AS and in all patients with undifferentiated SpA or PsA.⁶ A prospective study has recently reported the efficacy and tolerability of etanercept in 23 patients with AS who were resistant or intolerant to previous infliximab treatment. In particular, a 54-week Assessment in Ankylosing Spondylitis (ASAS) 20, ASAS 50, and ASAS 70 response rate was reported in 74%, 61%, and 39% of patients, respectively.⁷ In the present study, we evaluated the efficacy of switching between TNF α antagonists for patients with AS and PsA. Of the patients who switched from infliximab to



etanercept, a clinical response was seen after 3 months in 83% of patients with AS (BASDAI 50) and in 70% of patients with PsA (PsARC). Of the patients with PsA who switched from etanercept to adalimumab, 57.1% showed a clinical response. Patients who switched because of AEs and those who changed because of inadequate efficacy presented a similar clinical response. Hence, our data concur with previous studies on RA, in which a better response to a second TNF α antagonist was observed in most patients, regardless of the reason of failure of the previous treatment.³⁻⁵ In our population, 81.3% of patients

who had switched from infliximab to etanercept continued the treatment. Conversely, only 57.1% of patients who had changed from etanercept to adalimumab maintained the treatment. Interestingly, two of the three patients who stopped adalimumab because of inadequate response had already failed the other two TNF α antagonists. This observation seems to confirm previous data on RA patients, suggesting that the failure of two TNF α inhibitors predicts ineffectiveness to the third.¹⁵

There are some limitations to our study. First, it was a prospective, observational design without randomisation of

treatment options. Second being a real-life study, the decision to withdraw one TNF α antagonist and to switch to another depended only on the treating doctor's judgement.

In conclusion, the results of this study suggest that patients with SpA with inadequate response or AEs to one TNF α antagonist may be successfully treated with another, regardless of the reason for switching. Considering the sample size and the design of this study, larger prospective trials are warranted in order to confirm this observation.

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