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Original article

Switching from infliximab or etanercept to adalimumab in resistant or intolerant patients with spondyloarthritis: a 4-year study

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Abstract

Objective. TNF-α antagonists, infliximab (INF), etanercept (ETA) and adalimumab (ADA), have been demonstrated to be effective in controlling symptoms in SpAs. The aim of this study was to investigate the possibility of using ADA as a second or third choice.

Methods. A retrospective study was conducted in patients with SpA treated with TNF-α blockers who switched from INF or ETA to ADA, for inefficacy or adverse events. Kaplan–Meier survival curves were plotted to determine the rates of continuation of the first treatment (INF or ETA) as compared with the rates of continuation of the second or third treatment with ADA.

Results. A total of 1619 patients with SpA were treated with INF (35.3%), ETA (43.7%) and ADA (20.9%). In this cohort, ADA was started in 38 (2.34%) patients as a second anti-TNF-α drug and in 9 (0.56%) as a third anti-TNF-α drug. In SpA patients who failed the first anti-TNF-α, for whatever reason, survival curves for ADA (as a second anti-TNF-α) were significantly better than survival curves for these same patients on their first anti-TNF-α (overall: $P < 0.0001$; INF: $P < 0.0011$; ETA: $P < 0.02$).

Conclusion. Our retrospective study, resulting from real-life experience, showed that SpA patients who fail to respond to a first agent, INF or ETA, respond to ADA as a second-line drug regardless of the reason for switching.

Key words: Anti-TNF drugs, Spondylarthropathies, Psoriatic arthritis, Ankylosing spondylitis.

Introduction

TNF-α antagonists, infliximab (INF), etanercept (ETA) and adalimumab (ADA), have been demonstrated to be effective in controlling symptoms in SpAs such as AS and PsA [1].

Nevertheless, in controlled and observational studies, a variable percentage of patients are non-responders or achieve only a partial response and do not reach the commonly used outcome measurements such as Psoriatic Arthritis Response Criteria (PsARC) or Assessment in Ankylosing Spondylitis (ASAS) response. Moreover, in an additional percentage of patients, the treatment is interrupted due to loss of efficacy or side effects over the

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follow-up period [1–9]. As observed in patients with RA [10, 11], in the case of treatment failure with one agent, switching to the other agent may also be useful in patients with SpA due to the different molecular structures and targets of available TNF-α blockers [12]. In particular, RA patients with a history of failure to INF or ETA respond to ADA [11], but these data cannot be extrapolated to SpA, where treatment continuation rates with ADA, after a first anti-TNF-α drug, are poorly defined. The primary objective of this retrospective study, based on real clinical practice with SpA patients, was to investigate the possibility of using ADA as a second or third choice, since there is a lack of data on this topic.

Patients and methods

A retrospective study was conducted in nine Italian secondary referral rheumatology centres (Rome, Cagliari, Milano, Napoli, Padova, Potenza, Prato, Reggio Emilia and Telese Terme), involved in the research studies of SpA. We collected data on efficacy and safety of patients with SpA treated with TNF-α blockers who switched from INF or ETA to ADA, for inefficacy or adverse events, and had a minimum of 6 months of follow-up from January 2005 to December 2008. Each patient met the European Spondylarthropathy Study Group criteria for the classification of all forms of SpA [13].

The reasons for stopping were classified as lack of efficacy, adverse events (AEs) or other reasons. The definition of failure for inefficacy was based on clinical evaluation according to ASAS/European League Against Rheumatism management recommendations in AS [14] and recommendations of the Italian Society for Rheumatology for the use of biologic (TNF-α blocking) agents in the treatment of PsA [15].

ADA (40 mg every other week) and ETA (25 mg twice a week) were given subcutaneously; INF was administered intravenously at 3–5 mg/kg at Weeks 0, 2 and 6, and then every 6–8 weeks, although the treating physician could have increased or decreased this dose or schedule when warranted. At the time of initiation of the biologic drug for the patients, the main patient data were collected on a data sheet that was developed by all rheumatologists involved in the present study. This data sheet included age, sex, diagnosis, disease duration, Bath AS Disease Activity Index (BASDAI) [16], clinical pattern (peripheral and/or axial), swollen (out of 66) and tender (out of 68) joints, ESR and CRP level. Details of past and present anti-rheumatic therapies, such as DMARDs, corticosteroids, NSAIDs or analgesics, and current comorbidities were also recorded.

Statistical analysis

Kaplan–Meier (KM) survival curves were plotted to determine the rates of continuation of the first treatment (INF or ETA) as compared with the rates of continuation of the second treatment with ADA. In KM survival curve calculation, we entered time until the subject was 'censored' or the 'event' occurred. The numbers under the KM curves represent the number of patients reaching that point in follow-up time. This finding does not imply that the patients withdrew from treatment. The difference between survival curves were determined by the log-rank test. $P < 0.05$ was considered significant.

Results

From January 2005 to December 2008, a total of 1619 patients with SpA were treated with INF [$n = 572$ (35.3%)], ETA [$n = 708$ (43.7%)] and ADA [$n = 339$ (20.9%)]. In this cohort, ADA was started in 38 (2.34%) patients as second anti-TNF-α drug, and in 9 (0.56%) as third anti-TNF-α drug. The baseline characteristics of this cohort of patients are shown in Table 1. No PsA patient withdrew from the first anti-TNF-α drug owing to inefficacy with regard to the skin disease.

The overall rate of discontinuation of ADA, after the first anti-TNF-α drug, was 17%, with four (8.5%) patients stopping the second or third drug due to inefficacy and four (8.5%) stopping the second or third drug due to an AE (Table 2). The AEs that led to treatment discontinuation were infections (three cases) and urticaria (one case). In

Table 1 The main demographic and clinical features of SpA patients switched to ADA

Patient number (AS/PsA/uSpA) ($n = 47$)	19/25/3
Female/male, *n*	18/29
Age, mean (range), years	46 (27–72)
Disease duration, mean (range), months	129.9 (3–364)
BASDAI, mean (S.D.)	5.89 (1.19)
Clinical pattern, *n* (%)	
Peripheral	14/29.8
Axial	13/27.7
Axial with peripheral arthritis	20/42.5
ESR, mean (S.D.), mm/h	32 (22)
CRP, mean (S.D.), mg/dl	1.46 (2.06)
Concomitant treatment, *n* (%)	
DMARDs	18 (38.3)
Prednisone	20 (42.5)
NSAIDs	24 (51.1)
Previous DMARDs, *n* (%)	40 (85.1)
First anti-TNF-α therapy withdrawal	
ETA, *n* (%)	23 (48.9)
Reason, *n* (%)	
Inefficacy	15 (32.0)
Adverse event	
Infections	1 (2.1)
Leucopenia	1 (2.1)
Angio-oedema	2 (4.2)
Rash	1 (2.1)
Crohn's disease	2 (4.2)
Uveitis	1 (2.1)
INF, *n* (%)	24 (51.1)
Reason, *n* (%)	
Inefficacy	16 (34.0)
Adverse event	
Infections	1 (2.1)
Infusion reaction	6 (12.8)
Thrombophlebitis	1 (2.1)

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Table 2 Outcome of SpA patients switched to ADA

Reason for switch	Outcome of patients with ADA		
	Still taking ADA at the end of December 2008, *n* (%)	Stopped for inefficacy, *n* (%)	Stopped for adverse events, *n* (%)
Inefficacy (*n* = 34)	30 (88.2)	2 (5.9)	2 (5.9)
AEs (*n* = 13)	9 (69.2)	2 (15.4)	2 (15.4)
Total (*n* = 47)	39 (83.0)	4 (8.5)	4 (8.5)

the remaining 39 (83%) patients, ADA treatment was effective according to AS and PsA recommendations [14, 15].

The overall rate of discontinuation due to inefficacy or AEs of ADA was 5.9% among patients who also discontinued their first agent because of inefficacy, compared with a rate of 15.4% among patients who discontinued their first agent because of an AE (Table 2). When all switched patients were compared according to their reason for switching (inefficacy or AEs), no differences in baseline characteristics were seen.

In SpA patients who failed the first anti-TNF-α, for whatever reason, KM life tables for ADA (as second anti-TNF-α) and KM life tables for these same patients on their first anti-TNF are shown in Figs 1–3. Log-rank test to compare survival curves showed that the probability curve of taking ADA was significantly better than that of all anti-TNF-α ($P < 0.0001$), INF ($P < 0.0011$) and ETA ($P < 0.02$).

Discussion

TNF-α antagonists (INF, ETA and ADA) have been demonstrated to be effective in SpA, with a clinical response rate ranging from 43 to 71% by BASDAI-50 in AS patients and from 62 to 87% by PsARC in subjects with PsA [1]. However, a significant proportion of patients withdrew from therapy because of failure or poor tolerability in AS [2–7] and PsA [2, 7].

In our study of SpA patients who failed the first anti-TNF-α, the retention rate of ADA was significantly higher than that of all anti-TNF-α (IFN or ETA) ($P < 0.0001$), INF ($P < 0.0011$) and ETA ($P < 0.02$) used as first drug in the same patients. These results agree with a previous observational study [7] that showed a high survival rate in second anti-TNF-α course in AS (0.95) and in PsA (0.81), confirming the usefulness of switching to ADA. Moreover, in our study, the response of ADA, subcutaneous fully human mAb, did not seem to be related to the chemical structure of the first TNF-α blocker (chimeric mAb or recombinant soluble TNF receptor). Thus, these results support that switching to ADA may also be rational due to the different chemical structures and mechanisms of action of available TNF-α blockers [12] and due to the evidence of beneficial effects reported in patients with

Fig. 1 KM life table for ADA treatment (second anti-TNF-α) *vs* INF or ETA (first anti-TNF-α) in 38 patients with SpA.

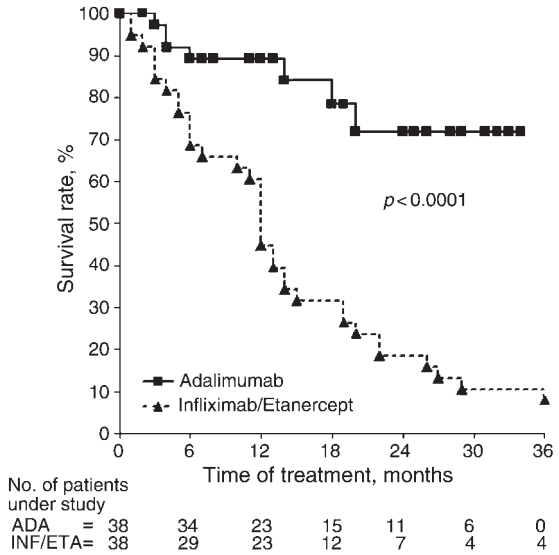
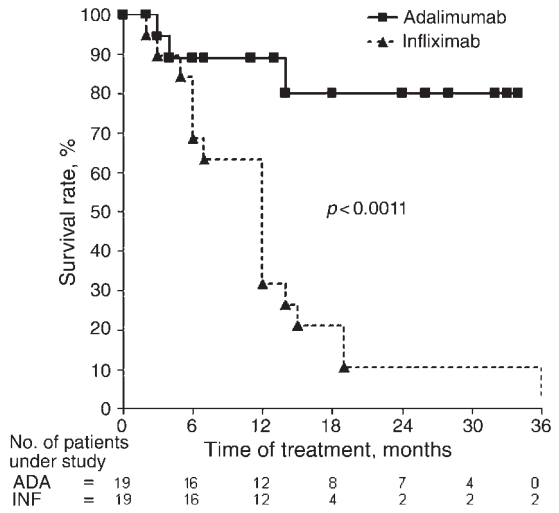


Fig. 2 KM life table for ADA treatment (second anti-TNF-α) *vs* INF (first anti-TNF-α) in 19 patients with SpA. *P*-value refers to the statistical difference between adalimumab and infliximab.



RA who fail to respond to INF or ETA [11, 17, 18]. Moreover, our data showed that the withdrawal rate of ADA, due to inefficacy (8.5%) or to an AE (8.5%), after switching, did not relate to the reason for failure of the previous treatment, as observed in RA studies [10, 18, 19].

Obviously, our results do not permit us to establish whether ADA is superior to other TNF-α blockers owing to the lack of a comparative analysis. Nevertheless, in SpA, the currently available data are few and they

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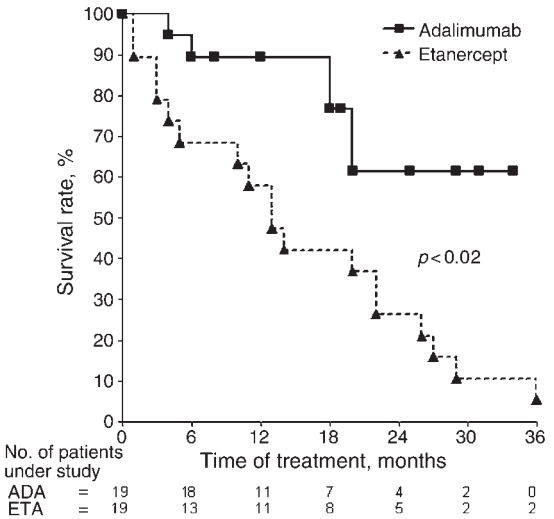
FIG. 3 KM life table for ADA treatment (second anti-TNF-α) *vs* ETA (first anti-TNF-α) in 19 patients with SpA. *P*-value refers to the statistical difference between adalimumab and etanercept.



consider INF or ETA mainly. In fact, a retrospective evaluation in 15 patients with SpA, switched from INF to ETA due to AEs or inadequate efficacy, showed a clinical response in 42.8% of the seven AS patients and in all subjects affected by uSpA or PsA [20]. A prospective study showed the efficacy and tolerability of ETA (50 mg/week) in 23 patients with AS resistant or intolerant to previous INF therapy [21]. In another study, among 16 patients who switched from INF to ETA, a clinical response was demonstrated in 83% of the AS patients and in 70% of the PsA patients [22]. In the same study, seven patients with PsA had switched from ETA to ADA but the analysis was only descriptive. Among 113 patients with AS, 15 patients (13%) switched to a second drug and 14 of these (93%) had a significant and sustained response [8]. In PsA, 90% of 60 patients achieved a significant response, using switching if required (20% of the cases) [9]. In these cohorts of SpA patients, the effectiveness of ADA as second or third anti-TNF-α agent has not been analysed. Interestingly, in our study, the probability curve of taking ADA as a second anti-TNF-α was not significantly different from that of ADA as third anti-TNF-α drug. This observation does not seem to confirm previous data on RA patients, where the failure of two TNF-α inhibitors predicts ineffectiveness for the third [23]. However, in our study, the number of patients who were given ADA as third anti-TNF-α therapy was too low to allow a definite conclusion to be drawn on this issue.

In conclusion, our retrospective study resulting from real-life experience, showed that SpA patients who fail to respond to a first agent, for instance INF or ETA, respond to ADA as second-line drug, suggesting that switching from one TNF-blocker to another is efficacious, regardless of the mode of action. Therefore, switching to ADA seems to be a feasible option for SpA patients who failed with the other two TNF-α blockers, even if the design of this current study does not permit comparison of the three TNF-α blockers in the switched patients.

Rheumatology key messages

- SpA patients who fail to respond to a first anti-TNF-α agent, such as INF or ETA, respond to ADA.
- Switching from one TNF blocker to another is efficacious, regardless of the mode of action.

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