

# EFFICACY AND SAFETY OF ADALIMUMAB IN ANKYLOSING SPONDYLITIS: DATA FROM REAL LIFE

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## Abstract

**Rationale.** Data from controlled trials showed that adalimumab, a humanized anti-TNF monoclonal antibody, is effective and safe in the treatment of ankylosing spondylitis (AS).

**Objectives.** The present study aimed to observe the efficacy and safety of adalimumab in AS in a real life clinical setting.

**Methods.** The study observed cross-sectionally and retrospectively the efficacy and safety of adalimumab in all the patients admitted to the Rheumatology Department of "Sfânta Maria" Clinical Hospital between January 2008 and June 2013 who were classified as having AS according to the modified New York criteria. The diagnosis and follow-up of uveitic cases were done in the Ophthalmology Department of the Emergency University Hospital.

**Results.** Within the study time-frame, 79 AS patients met the inclusion criteria: 71 (89.9%) had adalimumab for at least 24 months; 8 (10.1%) switched from adalimumab to another biological, as follows: 3 (3.8%) because of serious adverse events, 3 (3.8%) were primary non-responders and 2 (2.5%) were secondary non-responders. The clinical response was fast: after 3 months of treatment, 59 (83.1%) patients had BASDAI < 4 and 55 (77.5%) patients had BASFI < 4. Regarding safety, the serious adverse effects recorded were: infectious arthritis, pulmonary tuberculosis, pulmonary sarcoidosis. There were no cases of cancer or demyelinating disease during the study frame.

**Conclusions.** Therapy with adalimumab in AS produces a prompt and lasting effect. The efficacy (remission) and safety (adverse events) of adalimumab can be monitored in the real-life clinical setting using BASDAI, BASFI, and routine clinical evaluations. Clinicians may need to expect a slightly higher rate of serious adverse events and rate of treatment discontinuation than those reported by controlled trials.

**Keywords:** adalimumab, ankylosing spondylitis, efficacy, safety

## Abbreviations

ASAS – Assessment of SpondyloArthritis international Society

AS – Ankylosing spondylitis

BASDAI – Bath Ankylosing Spondylitis Disease Activity Index

BASFI – Bath Ankylosing Spondylitis Functional Index

CRP – C reactive protein

ESR – erythrocyte sedimentation rate

f – female

HLA – human leukocyte antigen

m – male

NSAID – non-steroidal anti-inflammatory drugs

TNF $\alpha$  – tumor necrosis factor  $\alpha$  inhibitors

## INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease which can involve the axial skeleton, the large peripheral joint, the entheses and several extra-articular sites (e.g. uveitis, bowel disease, skin etc.). (1) Typically AS patients are in their third de-

cade of life and present inflammatory chronic back pain, sacroiliitis on imaging and human leukocyte antigen (HLA) B27. Without treatment, patients with AS can develop severe anatomical deformity (kyphosis by syndesmophyte formation), various degrees of functional impairment (limitation of lumbar

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flexion) and psychological distress, subsequently with poor quality-of-life outcomes and higher social costs.(2,3)These can be prevented or improved using appropriate therapy in the setting of a comprehensive and multidisciplinary management strategy. Clinically, there are four therapeutic measures which proved effective in AS: for the axial form, physical therapy, non-steroidal anti-inflammatory drugs (NSAIDs) and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) inhibitors; for the peripheral form sulfasalazine in addition to the afore mentioned drugs. While physical therapy is mandatory for good functional outcomes, irrespective of medical treatments regimes, (4) NSAIDs are effective for chronic pain and are shown to slow radiographic progression, (5) bearing in mind their major cardiovascular and gastrointestinal side effects. The effectiveness of TNF $\alpha$  blockers proved the major role played by this cytokine in the process of chronic inflammation. All the approved anti-TNF $\alpha$  agents (adalimumab, etanercept, infliximab, golimumab) seem similar regarding efficacy and safety in AS patients. (6) Due to costs and the lack of long term safety data, anti-TNF $\alpha$  agents are given to selected AS patients, which should be monitored thoroughly. (7) For this purpose, in the clinical setting physicians may use two simple disease indices, BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and BASFI (Bath Ankylosing Spondylitis Functional Index).

Adalimumab, a humanized anti-TNF monoclonal antibody, has proved to be very effective in AS compared to placebo, (8-10) in short term and in long term, (11,12) regardless of radiographic progression, (13,14) peripheral and non-articular involvement, (15-17) race, (18) and age. (19) The most frequent adverse effect reported by investigators was the higher risk of serious infections, including the risk of reactivating tuberculosis. (20) The present study aimed to observe the efficacy and safety of adalimumab in AS in a real life setting.

## MATERIALS AND METHODS

### Study design

The study was designed to observe in a cross-sectional and retrospective manner the efficacy and safety of adalimumab in all the AS patients admitted to Internal Medicine and Rheumatology Department of our hospital between January 2008 and June 2013, using medical records kept for each visit to the rheumatologist.

### Patients and data

All the AS patients included in the study met the following criteria: age above 18 years; Caucasian race; classification of AS according to the modified New York criteria; (21) no overlapping chronic inflammatory disease (e.g. psoriatic arthritis, reactive arthritis); anti-TNF $\alpha$  naïve before initiation of adalimumab; active disease, defined as BASDAI > 4 and/or BASFI > 4, which needed biological therapy according to the physician's opinion and to the Romanian guide to AS treatment, (22) which is in accordance with the ASAS/EULAR recommendations. (23) The informed consent was presumed from the written informed consent each patient gave for being admitted to a university clinic (clinical examination, blood tests, imaging studies). The data were collected anonymously and it included for each record: demographics (age, gender), inflammation (C-reactive protein – CRP; erythrocyte sedimentation rate – ESR), disease measures (disease duration; peripheral and non-articular involvement; HLA B27 status; BASDAI; (24) (BASFI), (25) treatment variables (duration, BASDAI and BASFI treatment response, side effects, switches to other drugs). The study was approved by the local ethics committee.

### Statistics

Normally distributed data were reported as means with standard deviations, while non-normally distributed data were reported as medians with. Differences were evaluated using non-parametric tests: binomial and  $\chi^2$  tests (or Fisher's exact test where appropriate) for nominal data; Mann-Whitney U and Kruskal Wallis tests for scale data. Correlation was established computing Spearman's coefficients. All tests were two-sided, were considered significant if  $p \leq 0.05$  and were done using SPSS Statistics v.17.0.1 for Windows (SPSS Inc., Chicago, U.S.A., 2008).

## RESULTS

### General characteristics

A total of 79 AS patients met the inclusion criteria. Of these, 71 (89.9%) patients had adalimumab treatment for at least 24 months within the study time-frame (Table 1). The other 8 patients switched from adalimumab to another biological within the study period, as follows: 3 (3.8%) because of serious adverse events (Table 3), 3 (3.8%) were primary non-responders and 2 (2.5%) were secondary non-responders (Table 4).

**TABLE 1.** The general characteristics of the adalimumab group (n = 71)

variable	yes	no	p
sex (m/f)	50 (70.4%)	21 (29.6%)	0.001
axial involvement	71 (100%)	0 (0%)	< 0.001
peripheral involvement	43 (60.6%)	28 (39.4%)	0.096
HLA B27	67 (94.4%)	4 (5.6%)	< 0.001
extra-articular involvement	18 (25.4%)	53 (74.6%)	< 0.001
uveitis	16 (22.5%)	55 (77.5%)	< 0.001
inflammation	27 (38.1%)	44 (61.9%)	0.057
long-term NSAIDs use	39 (54.9%)	32 (45.1%)	0.102
sulfasalazine	35 (49.3%)	36 (51.6%)	0.452
age (years)	39 (22 - 65)		
disease duration (years)	8 (1-39)		
ESR (mm/h)	12 (1-72)		
CRP (mg/L)	2.3 (0.2-67.6)		
BASDAI	1.6 (0 -7.05)		
BASFI	1.9 (0 -5.7)		

– axial involvement refers to sacroiliitis and vertebra involvement; peripheral involvement refers to the large diarthrodial joints; extra-articular involvement refers to past or present involvement of the eyes (uveitic), digestive (bowel disease) and/or skin (psoriasis); inflammation refers to ESR > 20/30 mm/h (depending on gender) and/or CRP > 5 mg/L; long-term NSAIDs use refers to their administration daily in the last month as reported by the patient after 6 months of adalimumab;

– variables are reported either as “absolute value (percentage)” or as “median (interval)” depending on their normal or non-normal distribution respectively; p values are significant if bellow 0.05 and they represent the significance of the binomial test, assuming a 50% pre-test probability;

**abbreviations:** m – male; f – female; ESR – erythrocyte sedimentation rate; CRP – C reactive protein; HLA – human leucocyte antigen; NSAIDs – non-steroidal anti-inflammatory drugs.

### Adalimumab efficacy

The 71 AS patients who had adalimumab for at least 24 months within the study frame had a favorable disease course, with a reduction in signs and symptoms which prompted the fall of the activity and functional indices, BASDAI and BASFI (Table 2). The clinical response was fast: by 3 months, 59 (83.1%) patients had BASDAI < 4 and 55 (77.5%) patients had BASFI < 4 (Fig. 1 and 2).

### Adalimumab safety

Of the 79 AS patients, 3 had serious adverse effects, which lead to the interruption of immunosup-

**TABLE 2.** The evolution of disease activity while on treatment with adalimumab (n = 71)

index	time from the first adalimumab administration				
	0 months	3 months	6 months	12 months	24 months
BASDAI	7.00 (5.07-9.95)	3.45 (0.00-7.90)	2.30 (0.00-8.20)	1.95 (0.00-7.37)	1.35 (0.00-6.80)
BASFI	6.72 (3.02-9.70)	3.95 (0.00-8.90)	2.6 (0.00-9.10)	1.95 (0.10-7.60)	1.02 (0.00 -7.50)

variables are reported either as “median (interval)”

pressive therapy and ultimately to the replacement of adalimumab with other anti-TNF $\alpha$  agents (Table 3). Of note, there were no cases of cancer or demyelinating disease during the study frame.

**TABLE 3.** Side effects reported for adalimumab (n = 79)

type	number	switch
infectious arthritis	1 (1.3%)	etanercept
pulmonary sarcoidosis	1 (1.3%)	etanercept
pulmonary tuberculosis	1 (1.3%)	infiximab
high liver enzymes	1 (1.3%)	no
generalized furunculosis	1 (1.3%)	no
fever at first administration	1 (1.3%)	no
injection site reactions	8 (10.1%)	no

### Persistency of adalimumab treatment

In the 24 months study frame, a total of 71 (89.9%) patients retained their adalimumab treatment, while the other 8 (10.1%) patients switched either to etanercept or infliximab because of side effects of lack of response to adalimumab (Table 4).

**TABLE 4.** Persistency of adalimumab treatment (n = 79)

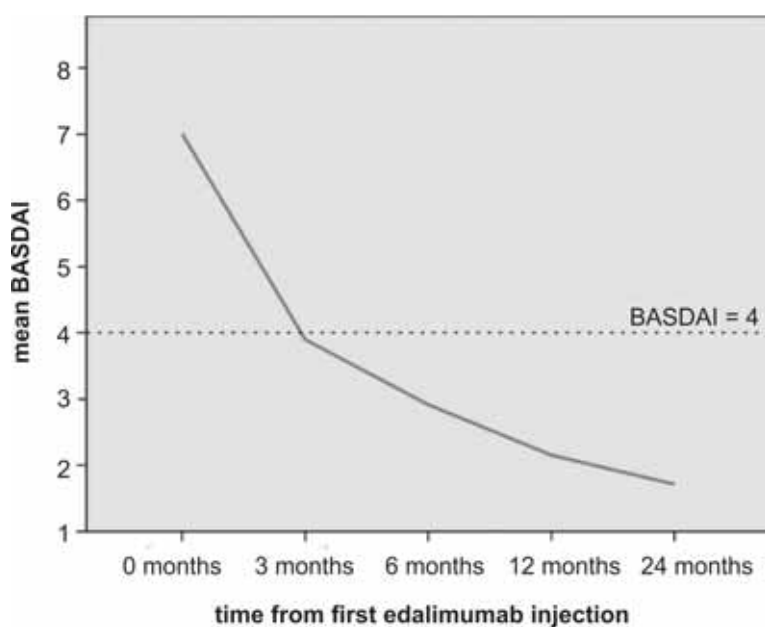
category	number	switch to etanercept	switch to infliximab
primary non-responders	3 (3.8%)	2 (66%)	1 (33%)
secondary non-responders	2 (2.5%)	0 (0%)	2 (100%)
adverse effects	3 (3.8%)	2 (66%)	1 (33%)
adalimumab retention	71 (89.9%)	–	–

primary non-responders are those patients who did not show a significant clinical and biological improvement after 3 months of therapy, as reported by the physician; secondary non-responders are those patients who, after an initial good response, the drug loses efficacy at any point during the treatment.

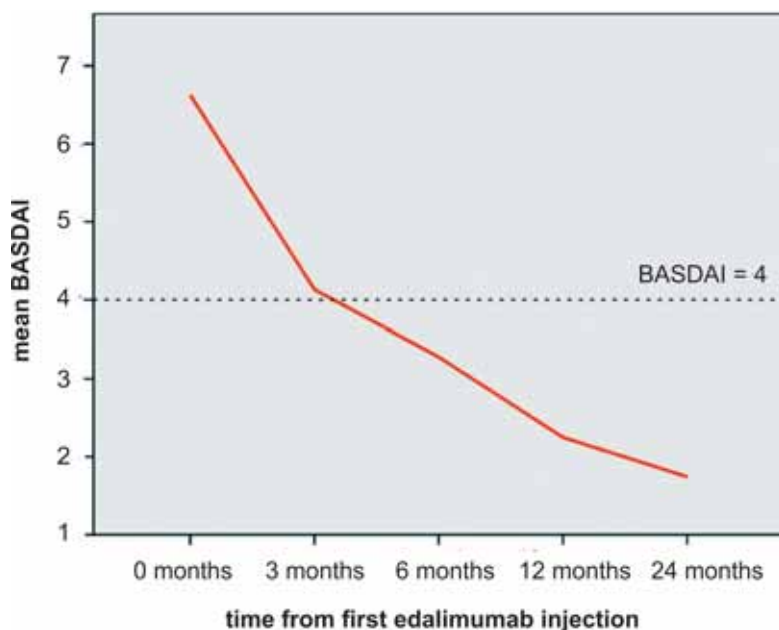
## DISCUSSION

### Main findings

In terms of efficacy, the study observed a prompt, lasting clinical effect of adalimumab in AS patients, as pointed out by the constantly decreasing values of BASDAI and BASFI. In terms of safety, we observed a 3.8% rate of serious adverse effects as re-



**FIGURE 1.** The 24 months evolution of disease activity according to BASDAI of the 71 patients treated with adalimumab



**FIGURE 2.** The 24 months evolution of functional impairment according to BASFI of the 71 patients treated with adalimumab

ported by physicians (infectious arthritis, pulmonary sarcoidosis, and pulmonary tuberculosis), where serious adverse effects meant those conditions attributed to adalimumab which needed hospitalization and specific multidisciplinary medical management. Almost 90% of the selected patients still had adalimumab after 24 months from its initiation, with a primary non-responder rate of 3.8% and a secondary non-responder rate of 2.5%.

### Comparing with other studies

In a recent meta-analysis, Wang et al. reviewed the safety and efficacy of adalimumab in AS patients

from randomized, placebo controlled and double-blind trials.<sup>(10)</sup>In one of their meta-analytic model of 787 AS patients treated with adalimumab, the BASDAI at 12 and 24 weeks was significantly lower in the adalimumab group compared to the placebo group. Our results also showed that by 3 months most of the responding patients had a BASDAI < 4. As for safety of adalimumab, the cited authors found a 55.3% rate of any adverse events during adalimumab treatment (17.7% in our study), a 1.9% rate of serious adverse events (3.8% in our study), and a 10.9% rate of injection site reactions (10.1% in our study). The lower rate of any adverse events in our



study compared to the above-mentioned meta-analysis can be explained by the fact that physicians in a real life clinical setting do not always record the mild complains of the patients, such as headaches, nausea etc. The fact that we recorded a higher rate of serious adverse events compared to the above-mentioned meta-analysis may be due to several situations: differences in the definition of “serious” adverse events; social-economic and education status of the patients; a selection bias manifest in the controlled studies which tends to exclude patients with severe structural damage and/or important comorbidities and which underestimates the true risk of serious adverse effects in the population. The same explanation can account for the differences in the rates of discontinuation of adalimumab treatment, 2% in the meta-analysis compared to 10% in our study.

### Study limitations

The study had several limitations which may raise some difficulties in interpreting the results. First of all, the retrospective design had to deal with missing data and follow-up shortcomings. The lack of strong end-points such as the ASAS criteria for treatment response would have been more appropriate to judge the efficacy of the drug, but these criteria are used more frequently in clinical trials than in real life settings. The lack of placebo and/or other biological drug arms did not allow comparisons with the respective comparators in order to more accu-

rately size the place of adalimumab in AS therapy. Finally, the small sample size impeded any regression models for determining significant predictors for clinical response.

### Conclusions

Therapy with adalimumab in AS patients in which NSAIDs and/or sulfasalazine are insufficient is an efficacious and safe therapeutic option, which produces a prompt and lasting clinical effect, in accordance with the new treat-to-target principles in AS. In this sense, the efficacy (remission) and safety (adverse events) of adalimumab treatment can be monitored in the real-life clinical setting using the two simple activity and functional indices, BASDAI and BASFI, and regular clinical and biological examinations. The thorough monitoring of AS patients treated with adalimumab ensures the early detection of side effects and non-responsivity. Clinicians may need to expect a slightly higher rate of serious adverse events and a slightly higher rate of treatment discontinuation than those reported by controlled trials.

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