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Arends, S.; Brouwer, Liesbeth; Efde, Monique; van der Veer, E.; Bootsma, H.; Wink, F.; Spoorenberg, A.

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S. Arends[1,2], E. Brouwer[1], M. Efde[2], E. van der Veer[3], H. Bootsma[1], F. Wink[2], A. Spoorenberg[1,2]

[1]Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, The Netherlands; [2]Rheumatology, Medical Center Leeuwarden, The Netherlands; [3]Laboratory Medicine, University of Groningen, University Medical Center Groningen, The Netherlands.

Abstract

Objective

Randomised controlled trials and open-label extension studies have demonstrated the clinical efficacy and safety of tumour necrosis factor-alpha (TNF-α) blocking therapy in pre-selected study patients with ankylosing spondylitis (AS). Our aim was to investigate the 7-year drug survival and clinical effectiveness of etanercept treatment in AS patients in daily clinical practice.

Methods

Consecutive AS patients from the prospective observational GLAS cohort who started etanercept because of active disease were included and evaluated over 7 years according to a fixed protocol. Continuation of treatment was based on BASDAI improvement and/or expert opinion.

Results

Of the 89 included AS patients, 45 (51%) were still using etanercept at 7 years of follow-up. Reasons for treatment discontinuation were adverse events (n=22), inefficacy (n=13), or other reasons although good clinical response (n=9). Etanercept treatment resulted in a rapid (after 6 weeks) and sustained improvement in disease activity (BASDAI, ASDAS, CRP, physician GDA), spinal mobility, physical function (BASFI), quality of life (ASQoL), and extra-spinal manifestations (swollen joints, tender joints and tender entheses). Furthermore, concomitant NSAID or DMARD use decreased significantly during follow-up. At 7 years, low disease activity and remission were present in 67–73% and 29–30% of the 45 patients, respectively. Of the patients who discontinued etanercept, 18 switched successfully to a second or third TNF-α blocker during follow-up.

Conclusion

In a large cohort of AS patients treated with etanercept, approximately 50% continued this treatment for 7 years. Our broad evaluation of clinical endpoints proves the long-term effectiveness of etanercept treatment in daily clinical practice.

Key words

ankylosing spondylitis, etanercept, effectiveness, safety, daily clinical practice

Suzanne Arends, PhD
Elisabeth Brouwer, MD, PhD
Monique Efde, MD
Eveline van der Veer, PhD
Hendrika Bootsma, MD, PhD
Freke Wink, MD
Anneke Spoorenberg, MD, PhD

Please address correspondence to:
Suzanne Arends, PhD,
University Medical Center Groningen,
Rheumatology and Clinical Immunology
P.O. Box 30001,
9700 RB Groningen, The Netherlands.
E-mail: s.arends@umcg.nl

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Introduction

Ankylosing spondylitis (AS) is an auto-inflammatory rheumatic disease that predominantly affects the axial skeleton. Inflammation in combination with spinal osteoproliferation and bone loss can cause severe pain, spinal stiffness, and impaired functioning, which has large impact on daily activities and health-related quality of life. The disease usually starts in the second or third decade of life and onset after 45 years of age is rare. Disease activity persists for decades in most AS patients (1).

The conventional treatment for axial symptoms of AS patients consists of nonsteroidal anti-inflammatory drugs (NSAIDs) and physical therapy. There is no robust evidence that disease-modifying anti-rheumatic drugs (DMARDs) are effective for the axial manifestations, but especially sulfasalazine may be considered to treat peripheral arthritis. Tumour necrosis factor-alpha (TNF-α) blocking therapy is available for AS patients with persistently active disease, who do not respond to the conventional treatment regimen (2).

Randomised controlled trials (RCTs) have demonstrated that TNF-α blocking therapy is effective in controlling systemic inflammation and improving clinical assessments of disease activity and physical function in the majority of AS patients (3). Three open-label extension studies showed long-term drug survival of 48% after 8 years in 69 patients treated with infliximab (4), 62% after 7 years in 26 patients receiving etanercept (5), and 60% after 5 years in 208 patients treated with adalimumab (6). These studies showed persistent clinical efficacy of TNF-α blocking therapy on disease activity, physical function, and quality of life (4-6). However, these findings for etanercept are limited to a relatively small number of pre-selected study patients. Therefore, our aim was to prospectively investigate the 7-year drug survival and clinical effectiveness of etanercept treatment regarding disease activity, spinal mobility, physical function, quality of life, extra-spinal manifestations, and concomitant medication use in AS patients in daily clinical practice.

Methods

The present analysis was based on data from the Groningen Leeuwarden Ankylosing Spondylitis (GLAS) cohort. GLAS combines up-to-date quality of care with gathering long-term prospective follow-up data in a large cohort of AS patients. Since November 2004, consecutive AS outpatients who started TNF-α blocking therapy because of active disease at the University Medical Center Groningen (UMCG) and the Medical Center Leeuwarden (MCL) are included and followed according to a fixed protocol (7). For the present analysis, AS patients who started etanercept until December 2007 were selected, so at least 7-year follow-up data would be available. Patients were excluded if they had previously received TNF-α blockers.

All patients were over 18 years of age, fulfilled the modified New York criteria for AS (8), and fulfilled the Assessment of SpondyloArthritis international Society (ASAS) criteria to start TNF-α blocking therapy: active disease defined as Bath AS Disease Activity Index (BASDAI) ≥4 and/or based on expert opinion (2). Etanercept was administered as subcutaneous injection once (50 mg) or twice (25 mg) a week. Continuation of treatment was based on BASDAI improvement (≥50% or two units compared with baseline) and/or expert opinion. Reasons for treatment discontinuation were classified into the categories intolerance due to adverse events, inefficacy based on insufficient BASDAI response, or other reasons.

In case of stable low disease activity (BASDAI<4) on standard dose regimen, dose reduction of etanercept could be applied. Dose reduction consisted of extending the interval between 25 mg doses. The strategy was patient-tailored (step-by-step approach), where patients' preference was taken into account. Dose reduction was expressed as percentage from the standard dose regimen (9). Patients were allowed to receive concomitant medication as usual in daily clinical practice. The GLAS cohort was approved by the local ethics committees of the MCL and UMCG. All patients provided written informed consent according to the Declaration of Helsinki.

Clinical assessments

Patients were evaluated at baseline, after 6 weeks, after 3, 6, and 12 months, and then every 6 to 12 months. At every visit, disease activity was assessed using the BASDAI (on a scale of 0–10), patient and physician global assessment of disease activity (GDA; on a scale of 0–10), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and AS disease activity score (ASDAS) calculated from BASDAI questions 2, 3, and 6, patient GDA, and CRP. Physical examination included the spinal mobility assessments chest expansion, modified Schober test, occiput to wall distance, and lateral lumbar flexion. Furthermore, the number of swollen joints (range 0–44), tender joints (range 0–46), and tender entheses (range 0–48) were obtained. Physical function was assessed using the Bath AS Functional Index (BASFI; on a scale of 0–10) and quality of life using the AS Quality of Life questionnaire (ASQoL; on a scale of 0–18). Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs) was recorded.

Response to treatment

BASDAI50 response was defined as ≥50% improvement from baseline. ASDAS clinical important and major improvements were defined as ≥1.1 and ≥2.0 units improvement from baseline, respectively (10). ASAS20 response was defined as ≥20% improvement from baseline and an absolute improvement of ≥1 unit in at least 3 of the 4 domains: physical function (BASFI), spinal pain, patient's GDA, and morning stiffness (mean from BASDAI questions 5 and 6), with no worsening by more than 20% in the remaining domain. ASAS40 response was defined as ≥40% improvement from baseline and an absolute improvement of ≥2 units in at least 3 of the domains, with no worsening at all in the remaining domain. (11)

BASDAI<4, ASDAS<2.1, and CRP<5 mg/l were used as definitions of low disease activity. ASDAS<1.3 was interpreted as inactive disease (10). ASAS partial remission was defined as an absolute score of ≤2 in all 4 domains: physical function, spinal pain, patient's GDA, and morning stiffness (11).

Statistical analysis

Results were expressed as number of patients (%), mean ± standard deviation (SD) or median (range) for categorical, normally distributed and non-normally distributed data, respectively. Chi-Square test, Fisher exact test, Independent samples *t*-test, and Mann-Whitney U-test were used as appropri-

Table I. Baseline characteristics of the 89 AS patients who started etanercept treatment.

	All patients (n=89)	Continuing etanercept for 7 years (n=45)	Stopping etanercept AE / IE (n=35)	*p*-value*
Age (yrs)	42±10	41 ± 10	44 ± 9	0.232
Gender (male) (n, %)	66 (74)	38 (84)	22 (63)	0.027
Duration of symptoms (yrs)	16 (2-41)	13 (2-41)	18 (3-41)	0.047
Time since diagnosis (yrs)	9 (0-37)	7 (0-34)	9 (0-37)	0.247
HLA-B27+ (n, %)	74 (85)	40 (89)	27 (79)	0.245
History of IBD (n, %)	4 (4)	1 (2)	3 (9)	0.314
History of uveitis (n, %)	28 (31)	12 (27)	14 (40)	0.207
History of psoriasis (n, %)	8 (9)	5 (11)	3 (9)	1.000
History of peripheral arthritis (n, %)	31 (35)	17 (38)	13 (37)	0.954
Current NSAID use (n, %)	79 (89)	42 (93)	30 (86)	0.288
Current DMARD use (n, %)	20 (22)	12 (27)	8 (23)	0.696
BASDAI (range 0-10)	6.2±1.8	5.7 ± 1.6	6.8 ± 1.6	0.004
$ASDAS_{CRP}$	3.9±0.8	3.7 ± 0.8	4.0 ± 0.7	0.089
Patient GDA (range 0-10)	6.5±2.0	6.3 ± 2.0	6.8 ± 1.8	0.275
Physician GDA (range 0-10)	5.7±1.7	5.8 ± 1.7	5.6 ± 1.7	0.737
CRP (mg/l)	15 (2-99)	15 (2-99)	15 (2-62)	0.976
ESR (mm/h)	21 (2-101)	21 (2-101)	19 (3-76)	0.468
Chest expansion (cm)	3.1±1.8	3.3 ± 1.8	2.9 ± 1.8	0.329
Modified Schober test (cm)	2.5 (0.1-7.0)	2.0 (0.2-6.3)	2.9 (0.1-7.0)	0.090
Occiput to wall distance (cm)	5.0 (0.0-34.5)	7.5 (0.0-34.5)	5.0 (0.0-28.0)	0.267
Lateral spinal flexion (cm)	8.3±4.3	8.6 ± 4.2	7.6 ± 4.4	0.332
Swollen joints (range 0-44)	0 (0-25)	0 (0-15)	0 (0-3)	0.117
≥1 swollen joint	19 (21)	12 (27)	5 (14)	0.179
Tender joints (range 0-46)	1 (0-42)	1 (0-18)	1 (0-42)	0.633
≥1 tender joint	47 (53)	23 (51)	19 (54)	0.778
Tender entheses (range 0-48)	3 (0-20)	3 (0-20)	3 (0-19)	0.496
≥1 tender enthesis	71 (80)	33 (73)	30 (86)	0.179
BASFI (range 0-10)	6.1±2.0	5.8 ± 2.2	6.1 ± 1.6	0.488
ASQoL (range 0-18)	9.8±4.0	9.0 ± 3.5	10.9 ± 4.0	0.024

Values are mean ± SD or median (range) unless otherwise indicated. *continuing *vs*. stopping etanercept. AS: ankylosing spondylitis; AE: adverse events; IE: inefficacy; HLA-B27+: human leukocyte antigen B27 positive; IBD: inflammatory bowel disease; NSAID: non-steroidal anti-inflammatory drug; DMARD: disease-modifying anti-rheumatic drug; BASDAI: Bath AS Disease Activity Index; ASDAS: AS Disease Activity Score; GDA: global disease activity; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BASFI: Bath AS Functional Index; ASQoL: AS Quality of Life.

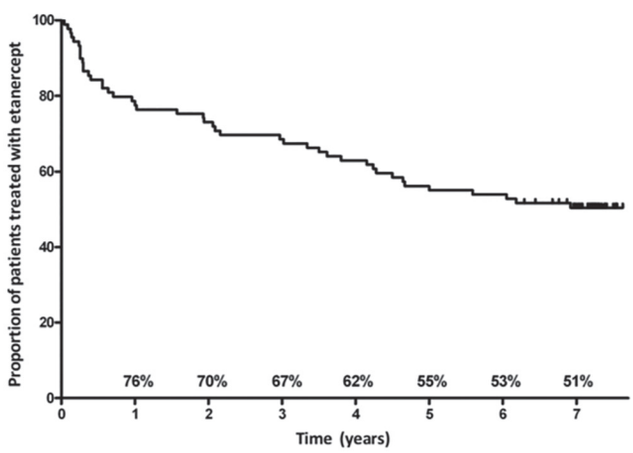

Fig. 1. Kaplan-Meier curve showing the proportion of AS patients treated with etanercept during 7 years of follow-up.

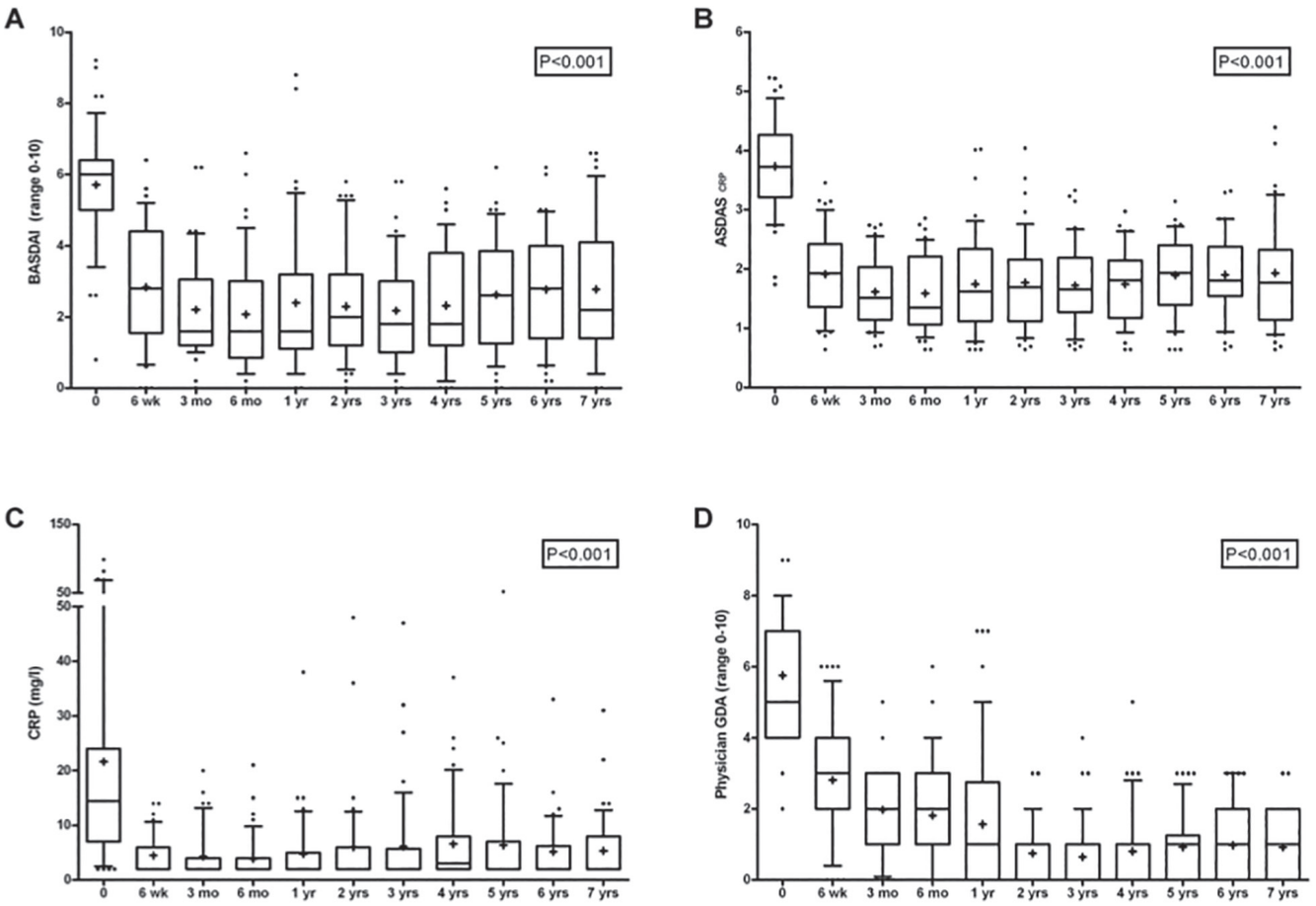

Fig. 2. Disease activity assessed with BASDAI (A), ASDAS (B), CRP (C), and physician GDA (D) in the 45 AS patients treated with etanercept for 7 years. Box-and-whisker plots: boxes indicate medians with interquartile ranges; + indicate means; whiskers indicate 10-90 percentile; • indicate outliers. *p*-values represent change over time.

ate to compare patient characteristics and clinical assessments at baseline between patients who continued and discontinued etanercept treatment because of adverse events or inefficacy. Generalised estimating equations (GEE) with exchangeable correlation structure was used to analyse clinical assessments over time within patients who continued etanercept for 7 years. If residuals were non-normally distributed, parameters were transformed (log or square root) before entered into the equation. *p*-values <0.05 were considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics 22 (SPSS, Chicago, IL, USA).

Results

Between November 2004 and December 2007, 89 AS patients started treatment with etanercept. Of these patients, 74% were male, mean age was 42±10 years, and median symptom duration was 16 years (range 2–41). Disease activity before start of etanercept was high, with mean BASDAI of 6.2±1.8 and mean ASDAS of 3.9±0.8. All patient characteristics are presented in Table I.

Drug survival

In total, 45 of the 89 (51%) AS patients completed the 7-year treatment period. As shown in Figure 1, of all 44 patients who discontinued etanercept, 21 stopped within the first year and 23 stopped spread in the next 6 years.

Patients who stayed on etanercept for 7 years were more frequently male (84% *vs*. 63%) and had relatively shorter symptom duration (median 13 *vs*. 18 years), lower BASDAI scores (mean 5.7 *vs*. 6.8) and lower ASQoL scores (mean 9.0 *vs*. 10.9) at baseline than patients who discontinued treatment because of adverse events or inefficacy (Table I). In the patients who stopped etanercept treatment, women had higher baseline BASDAI than men (median 7.8 *vs*. 6.5, *p*=0.07). In the patients who continued etanercept, baseline BASDAI was comparable between the sexes (median 6.0 *vs*. 5.9, *p*=0.60).

Clinical assessments during etanercept treatment

Etanercept treatment resulted in a rapid (after 6 weeks) and sustained improvement in disease activity in the 45 AS patients who continued this treatment for 7 years. For all assessments, the improvement was statistically significant at all follow-up visits compared to baseline values. From baseline to 7 years, mean BASDAI improved from 5.7 to 2.8, mean ASDAS from 3.7 to 1.9, mean patient GDA from 6.3 to 2.8, mean physician GDA from 5.8 to 0.9, median CRP from 15 to 2 mg/L, and median ESR from 21 to 9 mm/hr (Fig. 2; Table II).

Etanercept treatment also resulted in a rapid (after 6 weeks) and sustained im-

Table II. Clinical assessments over time in all 45 AS patients receiving etanercept for 7 years.

	Baseline	6 weeks	3 months	6 months	1 year	2 years	3 years	4 years	5 years	6 years	7 years
BASDAI	5.7 ± 1.6	2.8 ± 1.7	2.2 ± 1.4	2.1 ± 1.6	2.4 ± 2.0	2.3 ± 1.6	2.2 ± 1.5	2.3 ± 1.6	2.6 ± 1.6	2.8 ± 1.6	2.8 ± 1.9
ASDAS	3.7 ± 0.8	1.9 ± 0.7	1.6 ± 0.6	1.6 ± 0.6	1.7 ± 0.8	1.8 ± 0.8	1.7 ± 0.7	1.7 ± 0.6	1.9 ± 0.7	1.9 ± 0.7	1.9 ± 0.9
PatGDA	6.3 ± 2.0	3.0 ± 2.0	2.1 ± 1.5	2.5 ± 2.1	2.6 ± 2.4	2.4 ± 1.9	2.5 ± 1.9	2.3 ± 1.5	2.8 ± 1.7	3.1 ± 1.8	2.8 ± 2.3
PhyGDA	5.8 ± 1.7	2.8 ± 1.7	2.0 ± 1.2	1.8 ± 1.4	1.6 ± 2.0	0.8 ± 0.9	0.7 ± 1.0	0.8 ± 1.01	0.9 ± 1.0	1.0 ± 1.0	0.9 ± 1.0
CRP	15 (2-99)	2 (2-14)	2 (2-20)	2 (2-21)	2 (2-38)	2 (2-48)	2 (2-47)	3 (2-37)	2 (2-52)	2 (2-33)	2 (2-31)
ESR	21 (2-101)	5 (2-30)	5 (2-41)	6 (2-36)	6 (2-52)	10 (2-43)	9 (1-48)	10 (2-40)	9 (2-48)	12 (2-57)	9 (1-43)
CE	3.3 ± 1.8	3.9 ± 2.0	3.9 ± 2.0	4.1 ± 2.3	4.2 ± 2.1	4.6 ± 2.2	5.3 ± 2.6	5.9 ± 2.7	5.6 ± 2.9	4.8 ± 2.4	4.6 ± 2.3
MS	2.3 ± 1.5	2.9 ± 1.6	3.1 ± 1.8	3.1 ± 1.6	3.0 ± 1.6	3.1 ± 1.8	3.3. ± 1.6	3.4 ± 1.8	3.3 ± 1.9	3.4 ± 1.6	3.1 ± 1.5
OWD	7.5 (0-35)	4.8 (0-36)	4.0 (0-36)	4.0 (0-36)	4.3 (0-35)	5.0 (0-35)	4.0 (0-40)	4.5 (0-35)	5.0 (0-36)	4.8 (0-36)	5.0 (0-35)
LSF	8.6 ± 4.2	10.3 ± 5.5	10.7 ± 4.5	10.9 ± 5.0	10.9 ± 5.1	10.7 ± 5.0	11.3 ± 4.8	10.3 ± 4.5	11.1 ± 5.5	10.8 ± 5.1	11.1 ± 5.4
SJI	0 (0-15)	0 (0-14)	0 (0-10)	0 (0-2)	0 (0-2)	0 (0-2)	0 (0-1)	0 (0-3)	0 (0-1)	0 (0-1)	0 (0-2)
TJI	1 (0-18)	0 (0-15)	0 (0-12)	0 (0-11)	0 (0-12)	0 (0-7)	0 (0-7)	0 (0-20)	0 (0-17)	0 (0-14)	0 (0-14)
TE	3 (0-20)	1 (0-21)	1 (0-11)	1 (0-12)	0 (0-14)	0 (0-9)	0 (0-7)	0 (0-17)	0 (0-10)	0 (0-11)	0 (0-19)
BASFI	5.8 ± 2.2	4.0 ± 2.6	3.2 ± 2.5	3.0 ± 2.4	3.0 ± 2.5	3.0 ± 2.4	3.0 ± 2.4	3.0 ± 2.6	3.1 ± 2.4	3.2 ± 2.4	3.0 ± 2.3
ASQoL	9 (1-16)	5 (0-14)	4 (0-13)	3 (0-12)	3 (0-15)	2 (0-14)	3 (0-11)	3 (0-17)	3 (0-13)	4 (0-14)	2 (0-13)

Values are mean ± SD or median (range).
AS: ankylosing spondylitis; BASDAI: Bath AS Disease Activity Index (range 0-10); ASDAS: AS Disease Activity Score (including CRP); patGDA: patient global disease activity (range 0-10); phyGDA: physician global disease activity (range 0-10); CRP: C-reactive protein (mg/l); ESR: erythrocyte sedimentation rate (mm/h); CE: chest expansion (cm); MS: modified Schober test (cm); OWD: occiput to wall distance (cm); LSF: lateral spinal flexion (cm); SJI: swollen joint index (range 0-44); TJI: tender joint index (range 0-46); TE: tender entheses (range 0-48); BASFI: Bath AS Functional Index (range 0-10); ASQoL: AS Quality of Life (range 0-18). All assessments at all follow-up visits were significantly different from baseline (except for occiput to wall distance at 5 and 7 years, and tender joints at 6 weeks, 3 months, and 6 months).

provement in spinal mobility, physical function, and quality of life. For all assessments, the improvement was statistically significant at all follow-up visits compared to baseline values except for occiput to wall distance at 5 and 7 years (p=0.09). From baseline to 7 years, mean chest expansion improved from 3.3 to 4.6, median modified Schober test from 2.0 to 3.2, median occiput to wall distance from 7.5 to 5.0, mean lateral lumbar flexion from 8.6 to 11.1, mean BASFI from 5.8 to 3.0, and median ASQoL from 9 to 2 (Fig. 3; Table II). Furthermore, the number of swollen joints, tender joints, and tender entheses decreased significantly during etanercept treatment (Table II). The proportion of patients with ≥1 swollen joint decreased from 27% at baseline to 12% after 3 months and 2% after 7 years.

The proportion of patients with ≥1 tender joint decreased gradually from 51% at baseline to 20% after 7 years. The proportion of patients with ≥1 tender enthesis decreased gradually from 73% at baseline to 21% after 7 years.

The proportion of patients using NSAIDs decreased significantly from 93% at baseline to 44% after 3 months and remained stable during follow-up (36% after 7 years). The proportion of patients using DMARDs because of a history of peripheral arthritis decreased gradually from 27% at baseline to 7% after 7 years (Fig. 3).

Clinical response to etanercept treatment after 7 years

Of the 45 patients who were still treated with etanercept at 7 years of follow-up, BASDAI50 response was achieved in 56%, ASDAS clinical important improvement in 78%, ASDAS major improvement in 44%, ASAS20 response in 75%, and ASAS40 response in 57% at 7 years. Furthermore, 73%, 69%, and 67% of these 45 patients had low disease activity based on BASDAI<4, ASDAS<2.1, and CRP<5 mg/L, respectively. ASDAS inactive disease (score<1.3) was found in 29% and ASAS partial remission in 30% (Table III). All patients had low disease activity according to the physician (score<4) (Fig. 2).

At 7 years, 27 (60%) patients used etanercept 50 mg once per week (n=16) or 25 mg twice per week (n=11). The remaining patients had reduced etanercept to median 50% (range 35–78%) of the standard dose regimen.

Discontinuation of etanercept treatment

Reasons for treatment discontinuation were adverse events in 22 (50%) patients, inefficacy in 13 (30%), and other reasons in 9 (20%). The reasons to stop etanercept because of adverse events were recurrent infections (n=8), inflammatory bowel disease (IBD; n=4, one patient experienced also inefficacy), allergic skin rash (n=3), cardiac problems (n=2), iridocyclitis (n=1), bladder cancer (n=1), demyelisation problems (n=1), diarrhoea and increase in acne (n=1), and general malaise (n=1). Of the 13 patients who stopped etanercept because of inefficacy, most patients stopped within the first year of treatment (n=9). Other reasons to stop were one patient with good initial response; own choice, 2 women with pregnancy wish, 5 patients were lost to follow-up (Fig. 1). All these 8 patients showed good response to etanercept at their last visit. One patient deceased on a malignant astrocytoma.

Of the 44 patients who discontinued etanercept treatment, 24 switched to infliximab or adalimumab. At 7 years of follow-up, 18 patients still used their second (n=13) or third (n=5) TNF-α blocking agent, 3 patients had successfully restarted etanercept (discontinuation was because of IBD or pregnancy wish), and 6 patients did not use TNF-α blocking therapy (Fig. 1). The remaining 17 patients were lost to follow-up

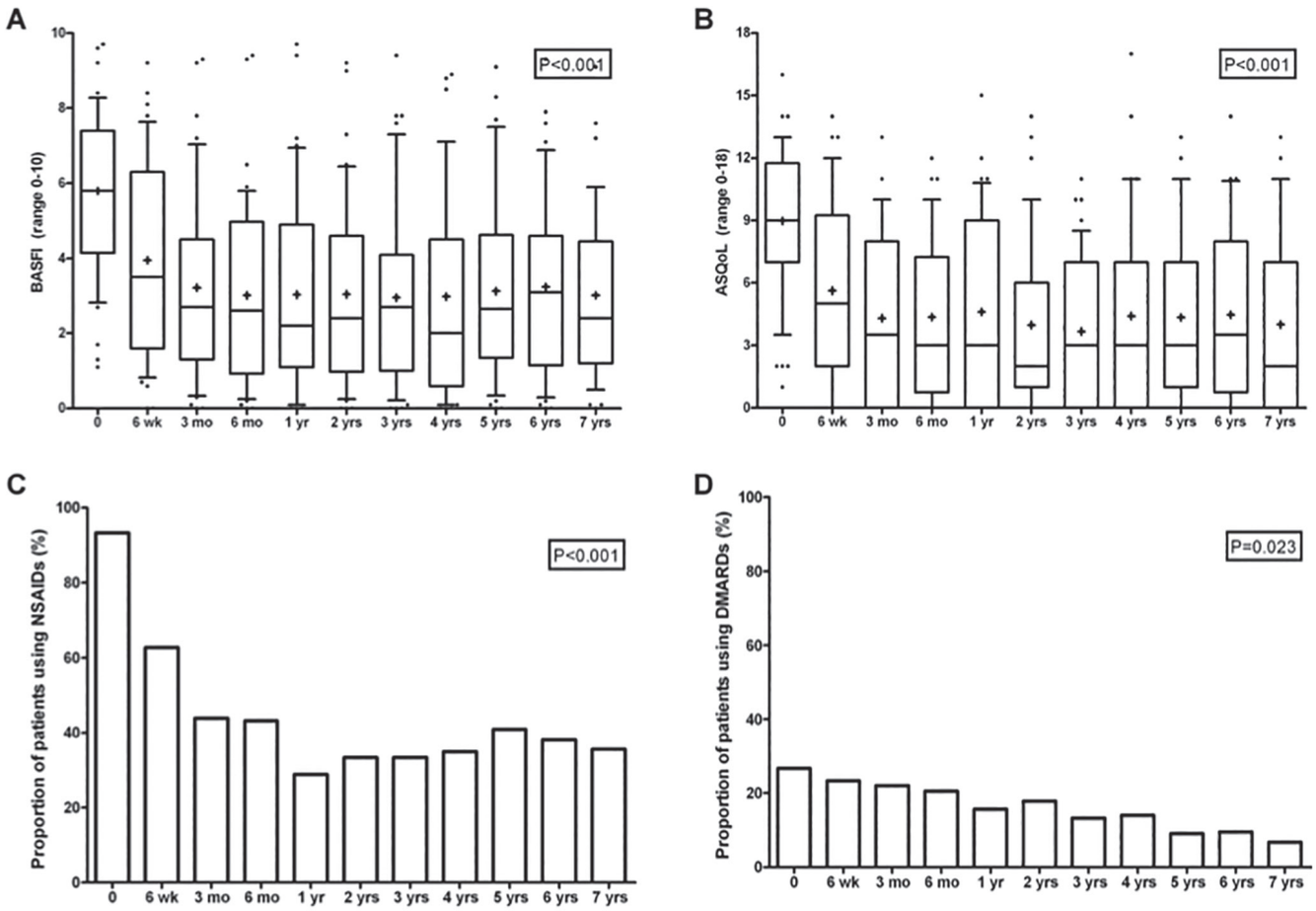

Fig. 3. Physical function assessed with BASFI (A), quality of life assessed with ASQoL (B), NSAID use (C), and DMARD use (D) in the 45 AS patients treated with etanercept for 7 years.
Box-and-whisker plots: boxes indicate medians with interquartile ranges; + indicate means; whiskers indicate 10-90 percentile; • indicate outliers.
p-values represent change over time.

after good response (n=5), discontinuation of TNF-α blocking therapy (n=11), or death (n=1; see above).

In the 18 patients who were still treated with infliximab (n=10) or adalimumab (n=8) at 7 years, disease activity improved significantly from baseline to 7 years; mean BASDAI from 6.6±1.6 to 4.7±2.1, mean ASDAS from 4.0±0.6 to 2.5±0.8, and median CRP from 14 (range 2–56) to 2 (range 2–10) mg/L.

Discussion

In this prospective observational cohort study, we investigated the long-term drug survival and clinical effectiveness of etanercept treatment in AS patients in daily clinical practice. In total, 51% of the 89 included AS patients were still using etanercept at 7 years of follow-up. Of the 44 patients who discontinued etanercept, approximately 50% stopped within the first year. In comparison, in an open-label extension study with etanercept, 81% of the 26 AS patients completed the 2-year and 62% completed the 7-year treatment period (5). As expected, slightly fewer patients continued etanercept in regular daily clinical practice than in preselected study patients. In patients who continued etanercept, disease activity such as BASDAI and ASDAS improved rapidly by 50% or more and sustained long-term. These findings are comparable with results from the small open-label extension study. Furthermore, ASAS response rates as well as the proportion of patients with low disease activity after 7 years of etanercept treatment were comparable (5).

Data from observational cohorts such as GLAS are important since these data reflect clinical practice. Inclusion criteria of RCTs with following open-label extension are often very strict and therefore data are not completely comparable to daily clinical practice. The standardised follow-up protocol of GLAS including patient characteristics, medication use and clinical assessments presents the unique opportunity to perform a broad evaluation of clinical endpoints, which is not possible in retrospective studies (12). In the 45 AS patients who continued etanercept treatment, a sustained improvement in disease activity was found according to the patient, the physician, and objective systemic inflammatory markers during 7 years of follow-up. Furthermore, spinal mobility, peripheral joint involvement, tender entheses, physical function, and quality of life improved significantly during etanercept treatment. Finally, the proportion of patients using concomitant NSAIDs or DMARDs decreased significantly during this long-term follow-up. Recently,

Table III. Response to treatment and disease activity status of all 45 AS patients receiving etanercept for 7 years.

	Baseline	7 years
Response to treatment		
BASDAI50	–	56% (25/45)
ASDAS CII	–	78% (32/41)
ASDAS MI	–	44% (18/41)
ASAS20	–	75% (33/44)
ASAS40	–	57% (25/44)
Disease activity status		
BASDAI<4	13% (6/45)	73% (33/45)
ASDAS<2.1	4% (2/44)	69% (29/42)
CRP<5	16% (7/44)	67% (29/43)
ASDAS<1.3	0% (0/44)	29% (12/42)
ASAS PR	0% (0/45)	30% (13/44)

BASDAI: Bath AS Disease Activity Index; ASDAS: AS Disease Activity Score (including CRP); CII: clinical important improvement; MI: major improvement; CRP: C-reactive protein; PR: partial remission.

the NSAID-sparing effect of etanercept was also demonstrated in a short-term 8-week RCT with NSAID intake as primary endpoint (13).

At 7 years, almost half of the patients had reduced their etanercept dose, *e.g.* to 25 mg once per week. These results are in line with previous studies which reported that dose reduction of etanercept is possible for maintaining clinical response in part of the AS patients (9, 14-16)

Patients who received etanercept for 7 years were more frequently male, had relatively shorter symptom duration, and had relatively lower BASDAI and ASQoL scores at baseline than patients who discontinued etanercept because of adverse events or inefficacy. In accordance, multiple studies have identified male gender as predictor of long-term continuation of TNF-α blocking therapy in patients with AS (17-21). In a recent cross-sectional study, we showed that female patients score significantly higher on patient-reported measures of disease activity (BASDAI, patient GDA, and tender joints), whereas objective measures of disease activity (CRP and swollen joints) were comparable between the sexes (22). Interestingly, in the present study, women who stopped etanercept treatment scored 1.3 point higher on baseline BASDAI than men. This indicates that there are differences in perception of disease activity between the sexes, which may negatively influence the response criteria to TNF-α blocking therapy in women.

Of the 44 patients who discontinued etanercept treatment, most patients stopped because of adverse events (50%), primarily recurrent infections, followed by IBD. Furthermore, 30% of these patients stopped because of inefficacy, mainly in the first year of treatment, and 20% due to other reasons not related to intolerance or inefficacy. The distribution of reasons for treatment discontinuation was comparable to data about TNF-α blocking therapy from registries (23, 24). Recently, a pooled analysis using data from five RCTs and four open-label studies in AS showed a favorable safety profile for etanercept, including serious infections, opportunistic infections, malignancies, non-malignant skin cancers, and disease-related IBD (25).

Approximately half of the patients who discontinued etanercept switched successfully to infliximab or adalimumab during follow-up. These findings are in line with previous studies which demonstrated that in case of side effects or insufficient response switching to another TNF-α blocker can be effective in AS (18, 26). Therefore, it is clinically very relevant to consider switching between TNF-α blockers in daily practice. Unfortunately, our long-term follow-up analysis of AS patients who discontinued etanercept was limited because one-third of these patients were lost to follow-up due to various reasons. Furthermore, the number of patients was too small to perform sub-analyses, *e.g.* to identify predictors of treatment discontinuation stratifying for inefficacy and adverse events.

In conclusion, approximately 50% of the AS patients continued etanercept for 7 years. Our broad evaluation of clinical endpoints proved the long-term good clinical effectiveness of etanercept treatment in daily clinical practice. The persistent improvements in disease activity, spinal mobility, physical function, and quality of life confirm the findings from the previous open-label extension study. Additionally, this prospective observational study demonstrates also an improvement in extra-spinal manifestations and a decrease in concomitant NSAID and DMARD use.

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