Is Etanercept 25 mg Once Weekly as Effective as 50 mg at Maintaining Response in Patients with Ankylosing Spondylitis? A Randomized Control Trial

Max Yates, Louise E. Hamilton, Frances Elender, Loretta Dean, Helen Doll, Alex J. MacGregor, Joegi Thomas, and Karl Gaffney

ABSTRACT. ***Objective.*** To investigate, in a pilot randomized controlled trial, whether etanercept (ETN) 25 mg once weekly is effective at maintaining a clinical response in patients with ankylosing spondylitis (AS) who have responded to the standard 50 mg dose.

Methods. Adults with AS not responding to conventional therapies were prescribed ETN 50 mg once weekly for 6 months. Responders as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were randomly assigned to taper to 25 mg once weekly or continue on 50 mg and followed for a further 6 months. The primary outcome measure was maintenance of a 50% reduction in the BASDAI or fall in BASDAI by ≥ 2 units and a ≥ 2-unit reduction in BASDAI spinal pain as measured on a 10-point visual analog scale at 6 months postrandomization.

Results. Of 89 patients assessed for eligibility, 59 were enrolled; 47 (80%) had sufficient clinical response and were eligible for randomization, 24 were assigned to continue receiving ETN 50 mg, and 23 to taper to 25 mg. After 6 months, 20 (83%) of the 50 mg arm maintained clinical response compared with 12 (52%) of the 25 mg arm (a difference of –31%, 95% CI –58% – –5%).

Conclusion. Although this pilot study demonstrates that treatment with ETN 25 mg was less effective at maintaining treatment response in the stepdown phase, 52% of participants maintained treatment response. Future research should address which patients are suitable for tapering. (J Rheumatol First Release June 1 2015; doi:10.3899/jrheum.141335)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS
ETANERCEPT
ANTI-TUMOR NECROSIS FACTOR THERAPY
RANDOMIZED CONTROL TRIAL

Ankylosing spondylitis (AS) is the prototypical spondyloarthropathy (SpA) and is characterized by sacroiliitis, spinal inflammation, and ankylosing, causing significant disability and reduced quality of life[1,2]. First-choice medical treatment for AS is with nonsteroidal antiinflammatory drugs (NSAID), although many patients do not achieve satisfactory clinical response with these agents alone[3,4]. A cross-sectional survey of 1080 patients revealed that 78% had regularly received NSAID during the previous year. Despite this, one-fifth of patients receiving NSAID still reported insufficient pain control and more than 40% changed their NSAID because of lack of efficacy[5]. Glucocorticoids and disease-modifying antirheumatic drugs that are used in other rheumatic diseases usually fail to achieve an adequate treatment response[6,7,8,9].

Etanercept (ETN) is a human recombinant version of the soluble p75 tumor necrosis factor (TNF) receptor that is linked to the Fc receptor of human immunoglobulin G subclass 1. It acts as a competitive inhibitor of the binding of TNF-α to cell-surface TNF receptors and thereby inhibits TNF-α–induced proinflammatory activity[10]. Anti-TNF-α drugs are effective biological therapies for AS and well established in clinical practice[11]. However, their high cost places considerable pressure on healthcare budgets. The standard recommended dose for ETN is 50 mg per week. While a lower dose can maintain a good treatment response in patients with rheumatoid arthritis[12,13], this requires further evaluation in patients with AS[14]. There have been several

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case series published on dose reduction of anti-TNF usage (either infliximab or ETN) in patients with AS. These studies have either been case series or retrospective analyses without prospective comparison to a control arm and performed without randomization[15,16,17,18,19,20,21,22]. In general, these studies revealed promising results regarding maintaining treatment response when the dose of anti-TNF was reduced.

The ANSWERS trial (ANkylosing Spondylitis With Etanercept RegimeS) is a pilot study addressing the lack of robust evidence regarding optimum treatment regimens[21,23,24]. It uses a pragmatic, open-label, parallel group, noninferiority, randomized controlled trial design to investigate whether clinical response is maintained in patients with AS when the standard dose of ETN is reduced from 50 mg to 25 mg. Maintenance of efficacy with a lower dose would have considerable cost-saving implications for healthcare budgets[25,26]. In addition, lower doses may lead to a reduced rate of adverse events (AE). The LOADET trial previously reported on doubling of the current licensed dose of ETN to 50 mg twice a week for 12 weeks[27]. There was a trend in the patients treated in the 50 mg twice weekly group having a greater rate of treatment-related AE. Of the participants assigned to 50 mg ETN twice weekly, 25 out of 28 participants had a treatment-related AE, as opposed to 18 out of 28 participants in the 50 mg once-weekly group.

Our primary objective was to investigate whether ETN 25 mg once weekly is effective in maintaining a clinical response in patients with AS who have responded to 50 mg once weekly. Our secondary objectives were to assess additional measurements of efficacy and adverse effects in standard and lower-dose groups.

Participants in the 25 mg arm who did not maintain a remission response were offered reinstatement of the standard 50 mg dose. Loss of remission response was defined as:

1. An increase in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of 2 or more units (or a 50% increase as referenced to the baseline score);
2. AND the increase in BASDAI was observed on at least 2 recall visits;
3. AND an increase in the spinal pain visual analog scale (VAS) of 2 cm or more;
4. AND the participant and physician considered reinstatement of the 50 mg dosage appropriate.

MATERIALS AND METHODS

Study participants. Eligible participants were adults aged 18–80 years recruited consecutively from outpatient clinics at 2 hospitals in the United Kingdom between November 2010 and September 2012. All participants fulfilled the modified New York Criteria for the diagnosis of AS[28]; had sustained, active spinal disease as measured by the BASDAI[29] (score ≥ 4); had not responded to 2 sequential NSAID; were biologic-naive; and were eligible for ETN according to UK prescribing guidelines[30]. Exclusion criteria were previous treatment with a biological therapy and/or any of the contraindications listed for ETN[31]. All participants started treatment with 50 mg ETN once weekly for 6 months. Responders as defined by reduction in BASDAI score (50% reduction in BASDAI or fall ≥ 2 units and a ≥ 2-unit reduction in BASDAI spinal pain measured on a 10-point VAS) after 6 months of standard dose ETN were randomly assigned (1:1) by an independent trial coordinated telephone system to taper to 25 mg or continue on 50 mg once weekly. Group allocation, stratified by site and longer lead-in period (see below), was carried out using permuted blocks of random size. Allocations were obtained by an interactive voice randomization system accessed by telephone. Both groups were followed for 6 months postrandomization.

Outcome measures. Measures of efficacy were collected at baseline and 3, 6, 9, and 12 months. Randomization was performed at 6 months.

The primary outcome measure was maintenance of clinical response postrandomization as indicated by the BASDAI (50% reduction, or fall ≥ 2 units and ≥ 2 unit reduction in spinal pain as measured on a 10-point scale) at 6 months postrandomization[29].

Secondary outcome measures were the following self-reported indices: assessment in AS response criteria [Assessment of Spondyloarthritis international Society (ASAS) 20, 40, 5 of 6, and partial remission], Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index, Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL), Ankylosing Spondylitis Disease Activity Score (ASDAS), Evaluating Ankylosing Spondylitis Quality of Life, standard measure of health outcome (EQ-5D), patient global disease activity, patient night pain, physician global disease activity, as well as C-reactive protein (CRP) levels and proportions of patients discontinuing therapy for different reasons (classified as "lack of efficacy," "toxicity," "both," and "other reasons").

Amendments to study protocol. The study protocol was amended to allow the lead-in period at 6 months to be extended by a further month if there had been evidence of clinical response at 3 months and presenting symptoms "on the day" were considered atypically poor because of extenuating circumstances. To minimize bias, participants requiring a longer lead-in (n = 9) were stratified in the randomization process to ensure equal distribution between trial arms.

Sample size. The target sample size was 50, 25 in each trial arm. Noninferiority in the 25 mg arm was defined *a priori* as 50% preservation of the clinical response as indicated by the BASDAI achieved in the 50 mg arm at 6 months after randomization. This equates to a –18.5% margin based on proportions observed in a previous study of 25 mg twice weekly in which ASAS20 response rates in placebo and ETN groups were 23% and 60%, respectively (i.e., 18.5% = 50% of 37%)[32].

Statistical methods. Demographic and clinical characteristics at baseline were compared between the treatment groups to identify any imbalances. The primary outcome measure, change in BASDAI score, was examined at each assessment both in terms of its continuous score and on the percentage of patients achieving a clinical response using chi-square statistics, Fisher's exact tests, and calculation of OR. Logistic regression was used to adjust for the 6-month score. Mixed-effects linear and logistic regressions, with study arm as a fixed effect and 6-month score as a random effect, were used to assess the overall difference between study arms post-tapering. Additional analyses were performed similarly on the secondary outcome measures. Both intention-to-treat (ITT) and per protocol (PP) analyses were conducted. Statistical significance was set at the 5% level ($p < 0.05$), and 95% CI were constructed around the main results.

Ethical approval for the study was granted by North West 2 REC Liverpool Central. Trial Registration: National Institute for Health Research National Research Register (public.ukcrn.org.uk/search, Study ID: 9375) and European Clinical Trials Database (eudract.ema.europa.eu/eudract-web/index.faces, EudraCT number: 2010-029013-10).

RESULTS

Baseline clinical characteristics. Progress through the phases of the study is depicted in Figure 1 [CONSORT statement (Consolidated Standards of Reporting Trials)]. Of the 89

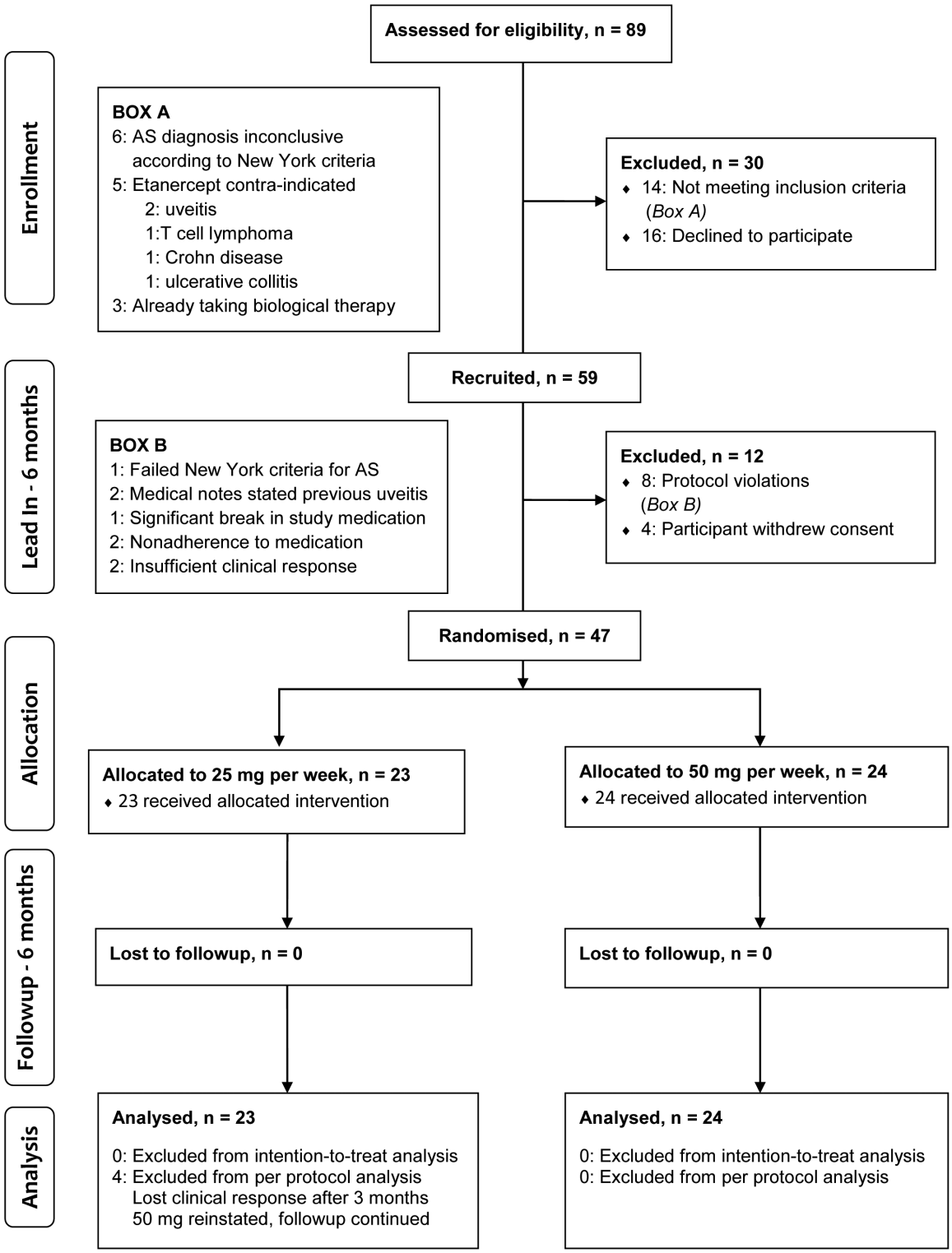


Figure 1. CONSORT diagram. CONSORT: Consolidated Standards of Reporting Trials; AS: ankylosing spondylitis.

patients assessed for eligibility, 59 patients were recruited; 47 (80%) of these patients had sufficient clinical response and were eligible for randomization with 24 assigned to continue on 50 mg ETN and 23 to taper to 25 mg. These 47 patients were the ITT dataset. Participants in the 25 mg arm who lost clinical response (n = 4) had the 50 mg dose reinstated and continued to be followed to the end of the study.

The 47 participants had a mean age of 46.7 years (SD 14.1, range 18–85), 41 (87.2%) were men, and their mean (SD) body mass index was 28.0 (4.76). Their mean (SD) BASDAI score was 6.83 (1.41), range 4.0–9.9, and mean (SD) ASQoL scores 11.1 (4.10), range 1–18. Their mean (SD) EQ-5D utility score was 0.46 (0.29), median = 0.60. There were no statistically significant differences between the 25-mg and 50-mg groups at baseline (Table 1). Adjusting for longer lead-in status did not alter the results.

Clinical response. Six months after randomization, 20 (83%) of the 24 patients in the 50 mg arm maintained clinical response compared with 12 (52%) of the 23 patients in the 25 mg arm (a difference of –31%, 95% CI –58% – –5%; Table 2). Noninferiority was not demonstrated in the stepdown arm (lower 95% CI = 70% of the observed effect). Adjusted BASDAI (p = 0.002), BASMI (p = 0.001), ASDAS (p = 0.007), ASAS night pain (p = 0.002), and global assessment scores (patient p = 0.009, physician p < 0.001) were also significantly higher in the 25 mg arm after tapering (Figure 2), with individuals less likely to maintain clinical response (OR 0.15, 95% CI 0.05–0.47), reach ASAS20 (OR 0.25, 95% CI 0.08–0.80), ASAS40 (OR 0.24, 95% CI 0.10–0.61), or achieve partial remission (OR 0.07, 95% CI 0.01–0.50) during followup (Table 3). Although 11 of the 23 had lost clinical response (as defined by failure to maintain BASDAI less than 50% of baseline value or reduction of 2

Table 1. Frequency of patients with each measure of outcome at each assessment by study arm and results of logistic regressions. Data are shown as n (%) unless otherwise specified.

Trial arm	3 Mos	6 Mos, Randomization	9 Mos	12 Mos
Clinical response*				
25 mg	14 (60.9)	23 (100)	14 (60.9)	12 (52.2)
50 mg	19 (79.2)	24 (100)	22 (91.7)	22 (91.7)
Chi-square p value	0.293	—	0.032	0.007
OR (95% CI)	0.41 (0.11–1.49)	—	0.14 (0.03–0.75)	0.10 (0.02–0.52)
Adjusted OR** (95% CI)	—	—	—	—
Mixed effects OR† (95% CI)			0.15 (0.05–0.47), p = 0.001	
ASAS20				
25 mg	13 (59.1)	18 (81.8)	10 (47.6)	14 (63.6)
50 mg	17 (81.0)	19 (90.5)	20 (90.9)	20 (90.9)
Chi-square p value	0.219	0.71 (0.66)‡	0.006	0.072 (0.069)‡
OR (95% CI)	0.34 (0.09–1.35)	0.47 (0.08–2.91)	0.09 (0.02–0.49)	0.18 (0.03–0.95)
Adjusted OR** (95% CI)	—	—	0.09 (0.02–0.56)	0.18 (0.03–1.15)
Mixed effects OR† (95% CI)			0.25 (0.08–0.80), p = 0.019	
ASAS40				
25 mg	10 (45.5)	12 (54.5)	8 (38.1)	10 (45.5)
50 mg	13 (61.9)	18 (85.7)	17 (77.3)	18 (81.8)
Chi-square p value	0.438	0.058 (0.045)‡	0.022	0.028 (0.027)‡
OR (95% CI)	0.51 (0.15–1.73)	0.20 (0.05–0.88)	0.18 (0.05–0.69)	0.19 (0.05–0.73)
Adjusted OR** (95% CI)	—	—	0.18 (0.04–0.78)	0.19 (0.04–0.87)
Mixed effects OR† (95% CI)			0.24 (0.10–0.61), p = 0.003	
ASAS5 of 6				
25 mg	9 (64.3)	12 (80.0)	6 (40.0)	9 (56.2)
50 mg	12 (66.7)	14 (77.8)	13 (65.0)	16 (94.1)
Chi-square p value	1.00	1.00 (1.00)‡	0.26	0.033 (0.017)‡
OR (95% CI)	0.90 (0.21–3.91)	1.14 (0.21–6.16)	0.36 (0.09–1.43)	0.08 (0.01–0.76)
Adjusted OR** (95% CI)	—	—	0.28 (0.06–1.36)	0.06 (0.01–0.83)
Mixed effects OR† (95% CI)			0.44 (0.17–1.11), p = 0.082	
ASAS partial remission				
25 mg	1 (4.3)	2 (8.7)	1 (4.3)	1 (4.3)
50 mg	4 (16.7)	4 (16.7)	8 (33.3)	7 (29.2)
Chi-square p value	0.37	0.70 (0.67)‡	0.031	0.061 (0.048)‡
OR (95% CI)	0.23 (0.02–2.21)	0.48 (0.08–2.89)	0.09 (0.01–0.80)	0.11 (0.01–0.99)
Adjusted OR** (95% CI)	—	—	0.00	0.08 (0.01–1.12)
Mixed effects OR† (95% CI)			0.07 (0.01–0.50), p = 0.008	

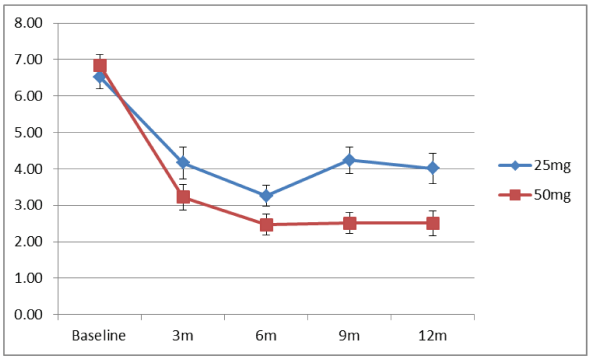
* 50% reduction in BASDAI score or change in BASDAI score of ≥ 2 points. ** Adjusted for 6-mo score. † Fixed effect for study group, random effect for 6-mo score. ‡ Fisher's exact test. ASAS: Assessment of Spondyloarthritis international Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

Table 2. Primary outcome measures at randomization and followup. Values are success/total n (%).

Outcome Measure*	Randomization, 6 Mos		Followup, 12 Mos	
	25 mg, n = 23	50 mg, n = 24	25 mg, n = 23	50 mg, n = 24
BASDAI score ≥ 50% reduction	12/23 (52.2)	20/24 (83.3)**	8/23 (34.8)	16/24 (66.7)**
BASDAI score ≥ 2-unit reduction	23/23 (100)	24/24 (100)	12/23 (52.2)	22/24 (91.7)***
BASDAI axial pain score ≥ 2-unit reduction	23/23 (100)	24/24 (100)	19/23 (82.6)	21/24 (87.5)
Complete clinical response†	23/23 (100)	24/24 (100)	12/23 (52.2)	20/24 (83.3)**

* Compared with baseline values. ** $p < 0.05$. *** $p < 0.01$ 25 mg vs 50 mg. † BASDAI score ≥ 50% reduction or BASDAI score ≥ 2-unit reduction and BASDAI axial pain score ≥ 2-unit reduction. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

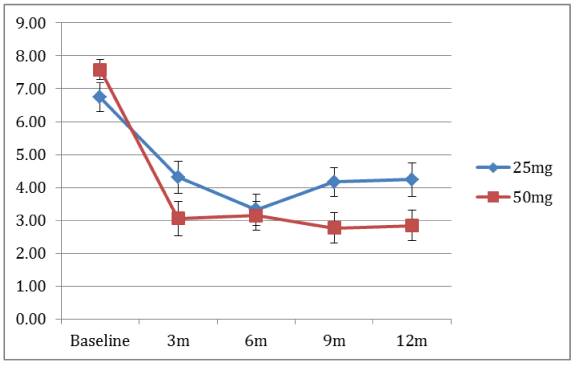
BASDAI



25 mg vs 50 mg post-6 mos

1.25 (95% CI 0.48–2.03), p = 0.002

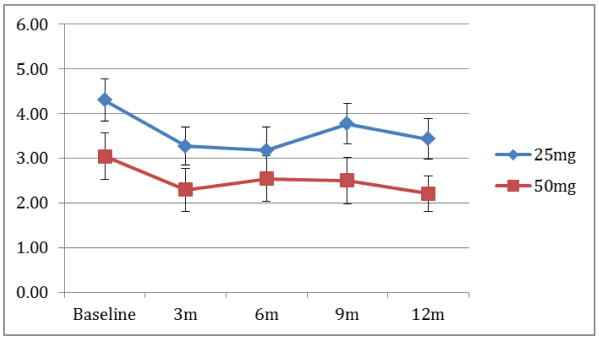
ASAS patient global assessment



25 mg vs 50 mg post-6 mos

0.97 (95% CI 0.24–1.70), p = 0.009

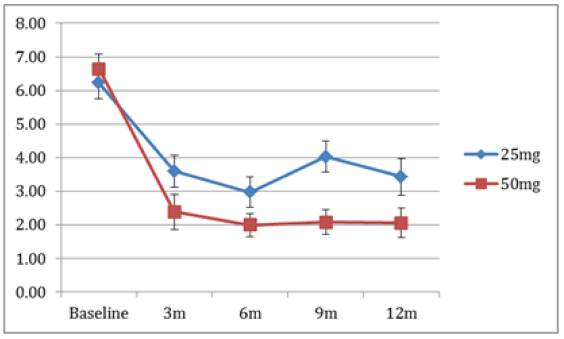
BASMI



25 mg vs 50 mg post-6 mos

0.56 (95% CI 0.24–0.87), p = 0.001

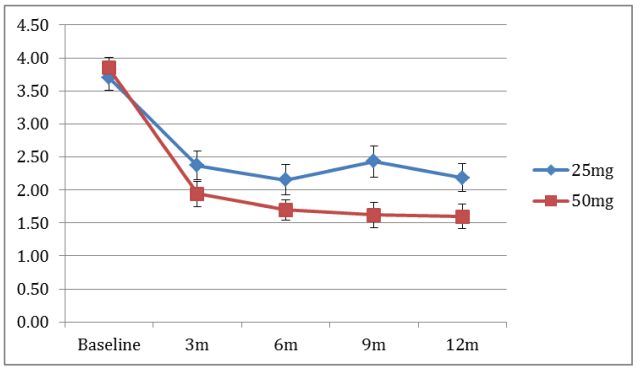
ASAS patient assessment of night pain



25 mg vs 50 mg post-6 mos

0.99 (95% CI 0.35–1.63), p = 0.002

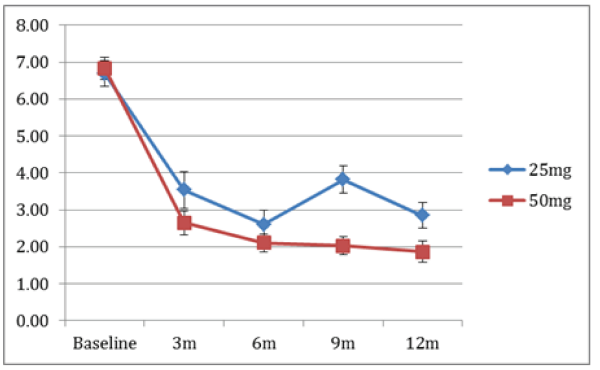
ASDAS



25 mg vs 50 mg post-6 mos

0.64 (95% CI 0.17–1.11), p = 0.007

ASAS physician global assessment



25 mg vs 50 mg post-6 mos

0.97 (95% CI 0.44–1.50), p < 0.001

CRP, mg/dl

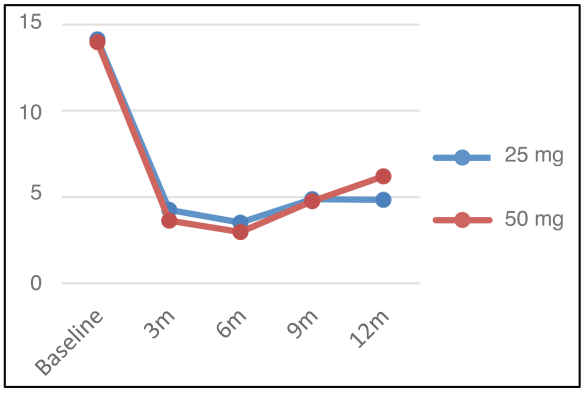


Figure 2. Mean (SE) scores on primary and key secondary outcome measures at each assessment by study arm and results of mixed effect linear regressions. Mixed effect refers to fixed effect for study group, random effect for 6-mo score. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASAS: Assessment of Spondyloarthritis international Society; BASMI: Bath Ankylosing Spondylitis Metrology Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein.

points and reduction of spinal VAS by 2 points) at 6 months, only in 4 participants did this occur on 2 consecutive followup visits and it was deemed appropriate for them to reinstate the 50 mg dosage. In those patients, 50% had regained their clinical response by the end of the study.

Details of AE. Table 4 provides details of AE recorded. This reveals 2 individuals in the 25 mg arm reported a high number of AE (n = 17 and 26). These AE account for 15% of the total number recorded, the majority not thought attributable to the study drug. The frequency and nature of AE are consistent with the Summary of Product Characteristics provided by the manufacturer of ETN and are not considered significant regarding patient safety or continuation of the trial.

DISCUSSION

We have shown, in the largest randomized controlled dose-reduction study of anti-TNF in AS, that clinical response is significantly less likely to be maintained when the weekly dose of ETN is reduced from 50 mg to 25 mg (difference –31%, 95% CI –58% – –5%). Both ITT and PP analyses were conducted; results did not differ. However, it should be noted that 52% of participants did maintain their treatment response once the dose of ETN was reduced.

This conflicts with previous studies that have limited inference as a consequence of their methodological approach, namely small sample size and complexity of design across multiple therapies[21,23,24]. Because this was a pilot study, the sample size of 25 per arm may be insufficient to demonstrate

Table 3. Secondary outcome measures at randomization and followup. Secondary outcome measures include the following self-report instruments: ASAS20, 40, 5 of 6, and partial remission; BASMI, BASFI, ASQoL, ASDAS, EASi-QoL, EQ-5D, patient GDA, patient night pain, physician GDA. CRP levels and proportions of patients discontinuing therapy for different reasons (classified as "lack of efficacy," "toxicity," "both," and "other reasons"). Values are mean (SD) median unless otherwise specified.

Outcome Measure	Randomization, 6 Mos		Followup, 6 Mos Postrandomization	
	25 mg, n = 23	50 mg, n = 24	25 mg, n = 23	50 mg, n = 24
ASAS20, n (%)	18/22 (81.8)	19/21 (90.5)	14/22 (63.6)	20/22 (90.0)
ASAS40, n (%)	12/22 (54.5)	18/21 (85.7)*	10/22 (45.5)	18/22 (81.8)*
ASAS5 of 6, n (%)	12/15 (80.0)	14/18 (77.8)	9/16 (56.2)	16/17 (94.1)*
ASAS partial remission, n (%)	2/23 (8.7)	4/24 (16.7)	1/23 (4.3)	7/24 (29.2)*
BASMI	3.17 (2.50) 2.00	2.54 (2.52) 2.00	3.43 (2.15) 3.00	2.21 (1.98)* 2.00
BASFI	4.20 (2.21) 3.90	2.51 (1.80)** 2.15	4.54 (2.19) 4.00	2.60 (2.17)** 2.13
ASQoL	6.63 (5.13) 5.00	4.33 (4.33) 3.50	7.27 (5.29) 6.00	4.96 (4.98) 3.00
ASDAS	2.15 (1.02) 1.85	1.70 (0.70) 1.49	2.18 (0.94) 2.02	1.60 (0.79)* 1.33
EASi-QoL				
Physical function	6.29 (3.47) 6.00	4.75 (3.22)* 3.50	6.83 (3.11) 6.00	5.21 (4.32)* 4.00
Disease activity	5.39 (2.55) 5.00	4.75 (3.22) 3.50	6.17 (2.90) 6.00	5.13 (3.70) 5.00
Emotional well-being	5.22 (4.31) 5.00	4.13 (3.88) 4.00	6.22 (5.11) 5.00	4.61 (4.21) 3.00
Social participation	5.78 (3.84) 6.00	4.65 (3.82) 5.00	6.45 (4.07) 5.50	5.61 (4.51) 5.00
EQ-5D VAS	7.09 (1.95) 8.00	7.55 (1.47) 7.10	5.94 (2.08) 6.50	7.04 (1.82) 7.20
Patient night pain	2.97 (2.18) 3.00	1.99 (1.66) 2.00	3.43 (2.66) 3.00	2.06 (2.19) 1.80
Patient GDA	3.33 (2.26) 3.00	3.14 (2.13) 2.75	4.24 (2.42) 3.00	2.84 (2.28)* 2.60
Physician GDA	2.60 (1.87) 2.10	2.11 (1.86) 2.10	2.85 (1.65) 2.60	1.87 (1.39)* 1.50
CRP, mg/l	3.51 (2.73) 2.99	2.95 (2.28) 2.99	4.82 (7.84) 2.00	6.21 (9.34) 2.99
Discontinuation of therapy, n***	0	0	4	0

* $p < 0.05$. ** $p < 0.01$ on Fisher's exact test (categorical data) or Mann-Whitney U test (continuous data). *** To be randomized, participants had to meet response criteria; 4 participants in the stepdown arm had their 50-mg dosage reinstated. ASAS: Assessment of Spondyloarthritis international Society; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life score; ASDAS: Ankylosing Spondylitis Disease Activity Score; EASi-QoL: Evaluating Ankylosing Spondylitis Quality of Life; VAS: visual analog scale; GDA: global disease activity; CRP: C-reactive protein.

Table 4. Adverse events (AE) by trial arm.

No. AE Per Participant	Trial Arm, n			Total Participants, n
	Lead-in	25 mg	50 mg	
0	11	1	0	12
1–5	8	7	9	24
6–10	3	7	5	15
11–15	2	2	2	6
16–20	0	1	0	1
21+	0	1	0	1
Total	24	19	16	59

AE	Trial Arm, n		
	Lead-in	25 mg	50 mg
Infectious complications	4	30	21
Injection site reaction	5	16	9
Itching/skin rash	1	4	1
Uveitis	2	3	0

noninferiority. For example, if there is no difference in observed trial arm clinical response proportions (group difference = 0), a sample size of 25 participants per group would have a 1-sided 97.5% CI whose lower boundary would be –23%.

The results of our study must be considered within the context of several limitations. First, there were significant differences between the groups for the outcomes measures even before the randomization timepoint. This can be seen from the 95% CI that, for all measures of outcome, does not include zero. It is, however, not recommended to conduct statistical tests at the point of randomization. This is because the most important point is whether the data differ between the groups after randomization, taking into account any imbalance at baseline that may or may not be statistically significant. Even if the apparent differences at baseline were not significant (and because of the small sample size this might be the case in our study), they should still be adjusted for in the analysis because they are clearly of clinical relevance. As can be seen in Table 1, there were highly statistically significant differences between the groups after adjusting for score at randomization in clinical response ($p = 0.001$), ASAS20 ($p = 0.019$), ASAS40 ($p = 0.003$), and ASAS

partial remission (p = 0.008); the difference in terms of ASAS5 of 6 was not significant (p = 0.082).

Second, our trial was conducted as an open-label study, which is compatible with standard clinical practice. The purpose of blinding is to prevent contamination of the allocated treatments, bias in the application of cotreatments, or bias in outcome assessment. In our trial, there was no evidence of difference between groups either in the number of patients that crossed over (i.e., received the treatment to which they were not randomized) or the receipt of adjuvant treatments (such as glucocorticoids or NSAID). Further, bias in the assessment of outcomes was possible because BASDAI relies on self-reported items. Participants' responses were not blinded to treatment allocation; therefore, they could have modified their responses depending on whether they believed that the reduced dose would work as effectively. However, this is also consistent with standard clinical practice and is, therefore, representative of the pragmatic approach we were aiming to achieve. In addition, biochemical values would not be affected by lack of blinding and it should be noted the reduction in CRP values was maintained in the stepdown phase (Figure 2). Of the patients randomized to the stepdown arm, over 50% maintained their clinical response. Finally, this trial was performed at 2 UK centers and therefore the results may not be readily extrapolated to other countries.

To our knowledge, this is the largest study designed to assess the effect of lowering the dose of ETN using a randomized control design. Although we did not demonstrate noninferiority, a proportion of patients randomized to the 25-mg group did maintain a clinical response. Larger studies are needed to identify the clinical characteristics of patients suitable for tapering.

The pragmatic study design (i.e., open label, "real-life experience", consecutive patients fulfilling the UK National Institute for Health and Care Excellence eligibility criteria for patient-centered outcomes) reflects UK clinical practice and maximizes the applicability of the results to usual care settings and prescribing decisions.

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REFERENCES

1. Carette S, Graham D, Little H, Rubenstein J, Rosen P. The natural disease course of ankylosing spondylitis. Arthritis Rheum 1983;26:186-90.
2. Ward MM. Quality of life in patients with ankylosing spondylitis. Rheum Dis Clin North Am 1998;24:815-27.
3. Zochling J, van der Heijde D, Dougados M, Braun J. Current evidence for the management of ankylosing spondylitis: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. Ann Rheum Dis 2006;65:423-32.
4. Song IH, Poddubnyy DA, Rudwaleit M, Sieper J. Benefits and risks of ankylosing spondylitis treatment with nonsteroidal antiinflammatory drugs. Arthritis Rheum 2008;58:929-38.
5. Zochling J, Bohl-Bühler MH, Baraliakos X, Feldtkeller E, Braun J. Nonsteroidal anti-inflammatory drug use in ankylosing spondylitis—a population-based survey. Clin Rheumatol 2006;25:794-800.
6. Kirwan J, Edwards A, Huitfeldt B, Thompson P, Currey H. The course of established ankylosing spondylitis and the effects of sulphasalazine over 3 years. Br J Rheumatol 1993;32:729-33.
7. Clegg DO, Reda DJ, Abdellatif M. Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondylarthropathies: a Department of Veterans Affairs cooperative study. Arthritis Rheum 1999;42:2325-9.
8. Chen J, Veras MM, Liu C, Lin J. Methotrexate for ankylosing spondylitis. Cochrane Database Syst Rev 2013;2:CD004524.
9. Chen J, Lin S, Liu C. Sulfasalazine for ankylosing spondylitis. Cochrane Database Syst Rev 2014;11:CD004800.
10. Goldenberg MM. Etanercept, a novel drug for the treatment of patients with severe, active rheumatoid arthritis. Clin Ther 1999;21:75-87.
11. Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2011;70:896-904.
12. Clunie G, Voules S, Watts R. Dose reduction of etanercept—can we treat more patients using a fixed budget? Rheumatology 2003;42:600-1.
13. Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque-Palazuelos F, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Lancet 2013;381:918-29.
14. Berthelot JM, Varin S, Cormier G, Tortellier L, Guillot P, Glemarec J, et al. 25 mg etanercept once weekly in rheumatoid arthritis and spondylarthropathy. Joint Bone Spine 2007;74:144-7.
15. Jois RN, Leeder J, Gibb A, Gaffney K, Macgregor A, Somerville M, et al. Low-dose infliximab treatment for ankylosing spondylitis—clinically- and cost-effective. Rheumatology 2006;45:1566-9.
16. Keeling S, Oswald A, Russell AS, Maksymowych WP. Prospective observational analysis of the efficacy and safety of low-dose (3 mg/kg) infliximab in ankylosing spondylitis: 4-year followup. J Rheumatol 2006;33:558-61.
17. Inman RD, Maksymowych WP; CANDLE Study Group. A double-blind, placebo-controlled trial of low dose infliximab in ankylosing spondylitis. J Rheumatol 2010;37:1203-10.
18. Lee SH, Lee YA, Hong SJ, Yang HI. Etanercept 25 mg/week is effective enough to maintain remission for ankylosing spondylitis among Korean patients. Clin Rheumatol 2008;27:179-81.
19. Lee J, Noh JW, Hwang JW, Oh JM, Kim H, Ahn JK, et al. Extended dosing of etanercept 25 mg can be effective in patients with ankylosing spondylitis: a retrospective analysis. Clin Rheumatol 2010;29:1149-54.
20. Mörck B, Pullerits R, Geijer M, Bremell T, Forsblad-d'Elia H. Infliximab dose reduction sustains the clinical treatment effect in active HLAB27 positive ankylosing spondylitis: a two-year pilot study. Mediators Inflamm 2013;2013:289845.
21. Navarro-Compán V, Moreira V, Ariza-Ariza R, Hernández-Cruz B, Vargas-Lebrón C, Navarro-Sarabia F. Low doses of etanercept can be effective in ankylosing spondylitis patients who achieve remission of the disease. Clin Rheumatol 2011;30:993-6.
22. Cantini F, Niccoli L, Cassarà E, Kaloudi O, Nannini C. Duration of remission after halving of the etanercept dose in patients with ankylosing spondylitis: a randomized, prospective, long-term, follow-up study. Biologics 2013;7:1-6.

23. Moghimi J, Sheikhvatan M, Semnani V. The use of low-dose etanercept as an alternative therapy for treatment of ankylosing spondylitis: a case series. Rheumatol Int 2012;32:2271-4.
24. Arends S, van der Veer E, Kamps FB, Efde M, Leijsma MK, Bootsma H, et al. Successful dose reduction of TNF-alpha blocking agents in ankylosing spondylitis patients with stable low disease activity. Ann Rheum Dis 2013;72 Suppl 3:A517.
25. Jois RN, Gaffney K, Keat A. Anti-tumour necrosis factor therapy for ankylosing spondylitis—unresolved issues. Rheumatology 2007;46:899-901.
26. Reveille JD, Ximenes A, Ward MM. Economic considerations of the treatment of ankylosing spondylitis. Am J Med Sci 2012;343:371-4.
27. Navarro-Sarabia F, Fernandez-Sueiro JL, Torre-Alonso JC, Gratacos J, Queiro R, Gonzalez C, et al. High-dose etanercept in ankylosing spondylitis: results of a 12-week randomized, double blind, controlled multicentre study (LOADET study). Rheumatology 2011;50:1828-37.
28. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
29. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286-91.
30. National Institute for Health and Care Excellence. Adalimumab, etanercept and infliximab for ankylosing spondylitis. [Internet. Accessed April 22, 2015.] Available from: www.nice.org.uk/guidance/ta143
31. European Medicines Agency. Enbrel. [Internet. Accessed April 22, 2015.] Available from: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000262/human_med_000764.jsp&mid=WC0b01ac058001d124
32. Calin A, Dijkmans BA, Emery P, Hakala M, Kalden J, Leirisalo-Repo M, et al. Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. Ann Rheum Dis 2004;63:1594-600.