Low dose etanercept treatment for maintenance of clinical remission in ankylosing spondylitis

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Abstract

Objective

To investigate the efficacy and safety of low-dose etanercept treatment after clinical remission of ankylosing spondylitis (AS) in the real world.

Methods

Data on 134 AS patients who were treated with etanercept for more than 12 months and achieved clinical remission (BASDAI<4 and CRP<0.5 mg/dL) were extracted from a large single centre registry. Drug survival and incidence of adverse events in 100 patients who reduced the dose during follow up (low-dose group) were compared with 34 patients who maintained the initial dose (standard-dose group). For minimisation of selection bias between the two groups, the same analyses were performed in a propensity score-matched population.

Results

Both groups showed similar BASDAI score and CRP levels during the follow-up. Drug survivals between the two groups were also comparable up to 4 years (vs. standard-dose group, adjusted HR=0.472, 95% CI 0.155–1.435). The same analysis performed after propensity score-matching showed concordant result. The incidence of injection site reactions in the low-dose group was significantly lower, and the incidence of other adverse events showed no differences between the two groups. In the low-dose group, dose reduction after more than 24 weeks of standard-dose treatment was associated with longer drug survival (adjusted HR=0.261, 95% CI 0.084–0.809).

Conclusion

Low-dose etanercept treatment after achieving clinical remission can be an alternative treatment option in terms of its comparable long-term efficacy and favourable safety in AS. More than 24 weeks of standard-dose treatment before dose reduction may be beneficial for longer drug survival in this strategy.

Key words

ankylosing spondylitis, TNFR-Fc fusion protein, clinical protocols

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Introduction

The introduction of tumour necrosis factor (TNF) inhibitors has strikingly changed treatment of ankylosing spondylitis (AS). Short- and long-term efficacy of these drugs has been demonstrated in numerous randomised clinical trials and cohort studies (1-5). The main goal of TNF inhibitor treatment in AS is to achieve clinical remission, since the effect of TNF inhibitors on radiologic progression is controversial (6). However, discontinuing TNF inhibitor treatment after remission usually leads to relapse within a few months (7). Therefore, AS patients who start TNF inhibitors are recommended to continue therapy, and this can be a substantial burden in terms of safety and cost (8, 9). Recently, some studies have suggested that low-dose TNF inhibitor treatment successfully maintained clinical remission in patients with AS (10-14). But these reports were mostly case series without a control group. In our clinical setting, dose-tapering of TNF inhibitors in the treatment of AS is often performed based on physician decision. So in this setting, it is suitable to directly compare the efficacy and safety of a tapering regimen with a conventional TNF inhibitor regimen in the real world.

Among the various TNF inhibitors used in AS, etanercept has advantages over other agents. First, it is self-injectable so more a flexible dose adjustment is possible. Second, since it was the first injectable TNF inhibitor approved for the treatment of AS in South Korea, investigation regarding long-term efficacy and safety is feasible. Finally, etanercept has a greater affinity for soluble TNF-α molecules and is less immunogenic (15-17). Because the two most common causes for discontinuation of etanercept treatment are clinical inefficacy and significant adverse effects, drug survival is a useful surrogate marker of effectiveness and safety. Therefore, in the present study, we investigated the long-term drug survival of low-dose etanercept in AS patients who achieved clinical remission and compared it with that of a conventional etanercept regimen. In addition, since there is no consensus on a dose-titration schedule for etanercept in AS, we also examined clinical factors, including optimal timing of dose reduction, that are related to longer drug survival.

Patients and methods

Patients

Data on AS patients were extracted from the AS registry from the Seoul National University Hospital. This single-centre registry includes data on 1,925 patients diagnosed with AS between January 2004 and December 2013. All patients fulfilled the modified New York and/or the Assessment of SpondyloArthritis International Society (ASAS) classification criteria at time of diagnosis (18, 19). Patients started etanercept for high disease activity (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] ≥4) despite adherence (Medication Possession Ratio [MPR] >80%) to non-steroidal anti-inflammatory drugs (NSAIDs) and/or disease-modifying anti-rheumatic drugs (DMARDs) for more than 3 months.

Patients who started etanercept between January 2004 and December 2013 and achieved clinical remission were initially included. Since the main objective of this study was to compare drug survival of the two treatment strategies in AS patients who achieved clinical remission, we restricted our analysis only to patients with: 1) more than 1 year of etanercept treatment and 2) at least 6 months of follow-up after dose reduction. Patients who did not fulfill these criteria were excluded (Fig. 1). Clinical remission was defined as BASDAI <4 and C-reactive protein (CRP) <0.5 mg/dL, based on a previous report (11).

Demographic and clinical features, including drug survival and dosing schedule of etanercept, were obtained from medical records. We also collected data on other medications prescribed before and after starting etanercept. This study was carried out in accordance with the Helsinki Declaration and was approved by the institutional review board (IRB) of Seoul National University Hospital (IRB No. H1310-085-528).

Patient assessment and dose adjustment of etanercept

Disease activity was evaluated using BASDAI and CRP. Patient visits for

clinical monitoring were performed after 3 months of treatment and every 6 months thereafter. All patients were assessed at each visit to continue etanercept treatment based on fulfillment of BASDAI 50 response criteria (19). Adherence to medication at baseline was estimated using the MPR of NSAIDs or DMARDs.

Because this study was observational, there was no consistent regimen for dose adjustment of etanercept, and four physicians in the rheumatology department independently decided on dose-tapering for their patients. However, all patients started etanercept at a dosage of 50 mg/week (25 mg twice weekly or 50 mg weekly) and dose reduction was considered only in patients who achieved clinical remission. Because there has been no consensus about dose adjustments in patients with a persistent low disease activity with conventional etanercept treatment, dose-tapering was not considered for them during the observation period. The first dose reduction was by 25 mg/week (25 mg weekly or 50 mg every other week) in all patients and further reduction was considered when clinical remission continued for the following 6 to 12 months. Temporary interruption or dose escalation of etanercept (<3 months) was allowed, but it was regarded as a discontinuation if this period exceeded 3 months. Patients in the standard-dose group switched to another TNF inhibitor without dose elevation for clinical inefficacy, which was as defined as a BASDAI >4 or a worsening of ≥2 units compared to the prior visit. With regard to safety, patients in both groups discontinued etanercept if grade 3 or recurrent grade 2 adverse events (defined as clinically significant adverse event [CSAE]) occurred.

Drug survival of etanercept

Drug survival was calculated as the duration of etanercept treatment, and all observation was censored on 31 December 2013. In this study, an event for drug survival was defined as a discontinuation due to clinical inefficacy or CSAE. Therefore, patients who stopped etanercept due to prolonged remission or pregnancy were censored at the date of discontinuation and not counted as events in the analysis.

Statistical analysis

Continuous values were presented as mean ± standard deviation or median (interquartile range) for normally and non-normally distributed data, respectively. Student's *t*-test or Mann-Whitney U test was used for the comparison of continuous data between the two groups. The correlation between two continuous values was assessed by Pearson's correlation coefficient. Kaplan-Meier curve and log-rank test were used to present crude drug survival between the two groups. Univariate and multivariate Cox regressions were performed to estimate hazard ratios (HRs) for discontinuation and to investigate clinical factors affecting drug survival. In the Cox proportional hazards model for comparison of drug survival between the two groups, the HR was adjusted for age, gender, disease duration, initial BASDAI score, baseline methotrexate (MTX) use and previous TNF inhibitor use (20). To minimise the impact of selection bias, we performed the same survival analyses in a propensity score-matched population. A propensity score was calculated using a multiple logistic regression model, including the following variables: age, gender, disease duration, initial BASDAI score, human leukocyte antigen (HLA)-B27, baseline CRP, baseline MTX use and previous TNF inhibitor use. Matching was performed using a caliper of 0.2 to remove poor matches. The incidence rate of adverse event during the observation period was expressed as the number of cases per 100 person-years (PYs). Differences in the incidence rates of adverse events between the two groups were assessed by Poisson regression. All statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA) and software R 2.8.0. *p*-values <0.05 were considered statistically significant.

Results

Characteristics of the patients

Data on 186 AS patients treated with etanercept were first extracted from our registry. Of these patients, 52 (28.0%) were excluded because they discontinued treatment within first 12 months, and there were no patients who maintained the reduced dosage for less than 6 months. Finally, 134 patients who showed a sustained clinical response for at least 12 months were analysed in this study. Among them, 100 patients received a reduced dosage of etanercept after achieving clinical remission (low-dose group), and the remaining 34 patients continued treatment at the initial dose (standard-dose group) (Fig. 1).

Thirty patients in standard-dose group and 92 patients in the low-dose group were first-time TNF inhibitor users. Patients in the low-dose group were significantly younger than those in standard group (37.0 years *vs*. 47.6 years, $p<0.001$), but there were no significant differences in other clinical factors such as BASDAI score, disease duration and HLA-B27 between the two groups. MPRs of NSAIDs or DMARDs at baseline between the two groups were also comparable (92.7±6.2% in standard-dose group *vs*. 91.8±5.2% in low-dose group, $p=0.491$) (Table I). During the observation period, 51 (38.3%), 23 (17.3%) and 16 (11.0%) patients used NSAIDs, MTX and sulfasalazine with etanercept, respectively, and their proportions between the two groups were comparable.

In the low-dose group, the median interval between starting etanercept and a dose reduction was 19.5 (25.1) weeks and most patients (91.0%) tapered the dosage within a year. The median proportion of the standard-dose period in total duration of etanercept treatment was 0.10 (0.17), and there were no patients with a ratio exceeding 0.5. This suggests that all patients in the low-dose group maintained a long-term low-dose period after a relatively short period of standard-dose treatment for clinical remission.

Baseline characteristics of patients after propensity score matching are described in Table I. There were no significant differences in patient age between groups, and other clinical factors were more balanced after matching (Supplementary Figure 1).

Disease activity during the observation

All patients achieved clinical remission within a year of etanercept treatment. Times to achieving clinical remission were not significantly different between groups (15.3±12.4 weeks in the standard-dose group *versus* 16.1±14.4 weeks in the low-dose group, p=0.779). Disease activity as indicated by BASDAI scores and serum CRP level was also similar between the two groups over all monitoring visits (Fig. 2). This result was concordant with the same analysis performed using the propensity-matched population (data not shown).

Drug survival of etanercept

The enrolled patients were observed for a total of 536.8 PYs (95.9 PYs with standard-dose group and 440.9 PYs with low-dose group), and the median duration of etanercept treatment was 43.1 (41.1) months. During follow-up, 6 (17.6%) patients in the standard-dose group and 22 (22.0%) in the low-dose group stopped etanercept due to adverse events or clinical inefficacy. CSAEs (21/28, 75.0%) were a more common cause of discontinuation than inefficacy (7/28, 25.0%), with a similar distribution between the two groups. In 116 censored patients, 24 patients were lost to follow-up (5 in the standard-dose group and 16 in the low-dose group), and 72 patients actively maintained etanercept at the end of data collection (22 in the standard-dose group and 50 in the low-dose group). Other censored patients discontinued treatment due to prolonged remission or pregnancy.

Overall 2-, 3- and 4-year drug survivals in the standard-dose group were 93.5%, 89.4% and 76.2%, respectively, compared with 98%, 91.0% and 83.4% in the low-dose group. Crude drug survival in the low-dose group was numerically higher than in the standard-dose group (p=0.282 by log-rank test). This result was maintained after adjustment for clinical factors (age, gender, disease duration, initial BASDAI score, baseline MTX use and previous TNF inhibitor use; adjusted HR = 0.472, 95% confidence interval [CI] 0.155-1.435, p=0.186) (Fig. 3A).

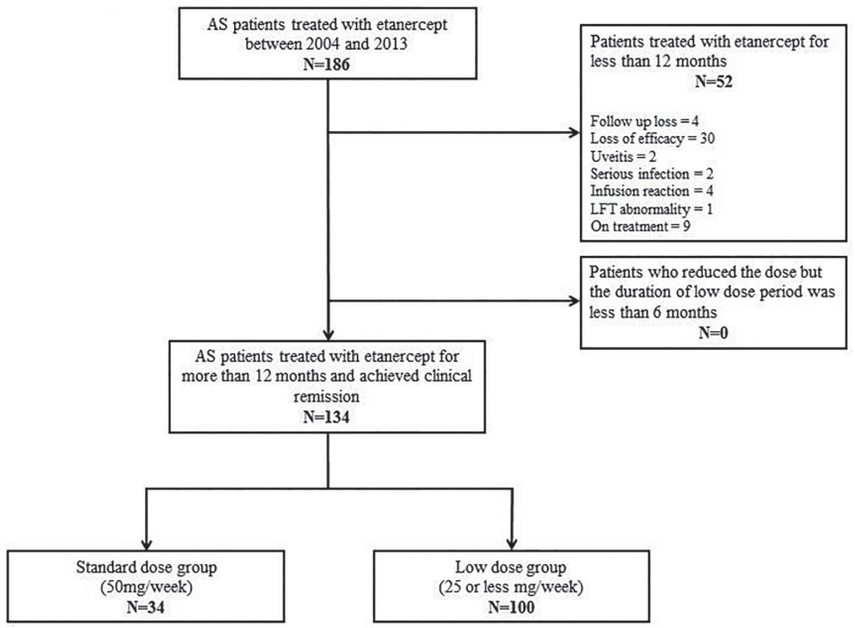

Fig. 1. Disposition of the patients in this study.

In the propensity score-matched population, 2-, 3- and 4-year drug survival rates for the standard-dose group were also similar to those of the low-dose group, but the numerical difference between the two groups decreased after matching (88.1% *vs*. 96.0%, 88.1% *vs*. 89.6% and 70.5% *vs*. 84.2% in 2-, 3- and 4-year drug survival, respectively, p=0.448 by log-rank test) (Fig. 3B). In the multivariate Cox proportional hazards model, the outcome was concordant with the results from the whole study population (adjusted HR = 0.619, 95% CI 0.194-1.973, p=0.417).

Incidence of adverse events

Incidence rates of any adverse events between groups were comparable but numerically lower in the low-dose group (54.2/100 PYs *vs*. 61.5/100PYs in the standard-dose group, p=0.397). Infection, predominantly upper respiratory tract, was most common in both groups (18.7/100 PYs in the standard-dose group *vs*. 21.5/100 PYs in the low-dose group, p=0.582). Incidence rates of other adverse events between groups were also similar; however, injection site reactions occurred less frequently in the low-dose group (2.7/100 PYs *vs*. 6.3/100 PYs in the standard-dose group, p=0.014) (Table II). CSAEs occurred in 23 patients and its incidence was not different between groups (5.2/100 PYs in the standard-dose group *vs*. 4.1/100 PYs in the low-dose group, p=0.783).

Clinical factors affecting drug survival in the low-dose group

Since there has been no consensus about an optimal schedule for dose reduction of etanercept in AS, we investigated clinical factors affecting drug survival in the low-dose group. Time to dose reduction was positively correlated with drug survival of etanercept (r=0.261, p=0.009). Interestingly, a subgroup of patients from the low-dose group who reduced the dose after more than 24 weeks of standard-dose treatment showed significantly longer drug survival than patients in the low-dose group with ≤24 weeks of standard-dose period (HR 0.250, 95% CI 0.083-0.756, p=0.014). This result was consistent in a multivariate model adjusted for age, gender, disease duration, initial BASDAI score, baseline MTX use and previous TNF inhibitor use (adjusted HR 0.261, 95% CI 0.084–0.809, p=0.020). Time to achieve clinical remission between the two subgroup was comparable (14.8±5.3 weeks *vs*. 12.9±6.3 weeks, p=0.131) and other demographic and clinical factors at the initiation of treatment also showed no between-subgroup differences. Previous TNF inhibitor use was associated with early discontinuation of low-dose etanercept treatment in multivariate

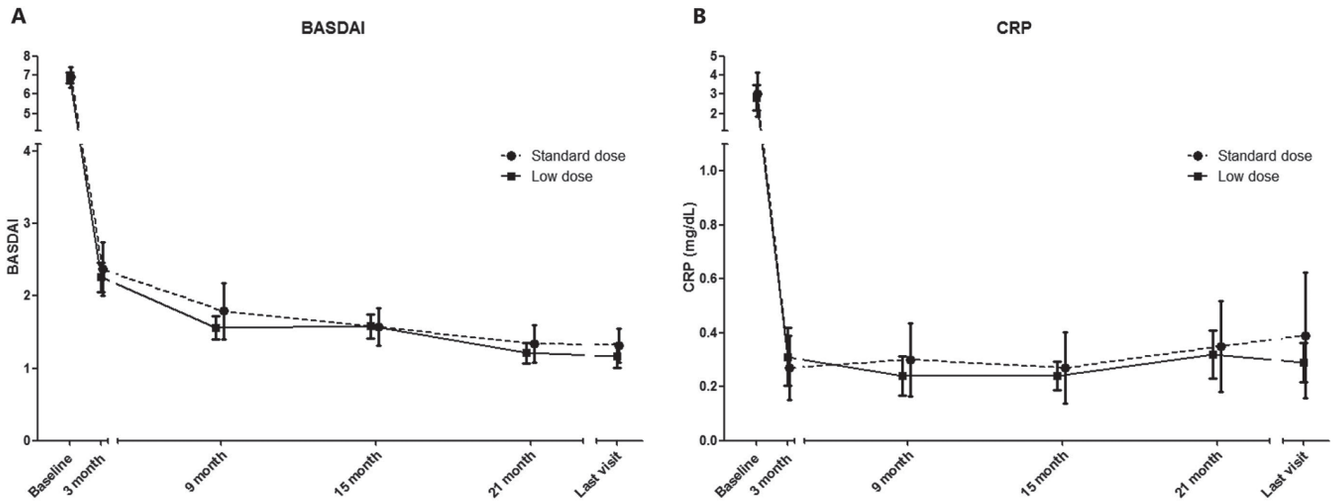

Fig. 2. Longitudinal changes of BASDAI (**A**) and serum C-reactive protein (**B**) between standard and low dose groups (mean, 95% confidence interval). These factors were not significantly different between two groups over the entire treatment period.

Table I. Baseline characteristics of patients.

	Whole population			Post-matched population		
	Standard-dose group n=34	Low-dose group n=100	*p*-value	Standard-dose group n=31	Low-dose group n=52	*p*-value
Female (n, %)	3 (8.8%)	23 (23.0%)	0.082	3 (9.7%)	6 (11.5%)	0.792
Age, mean (SD), years	52.0 (13.0)	42.8 (13.3)	<0.001	47.2 (13.7)	43.9 (12.6)	0.261
Disease duration, mean (SD), years	11.0 (7.6)	9.4 (4.8)	0.241	10.6 (7.4	10.6 (5.9)	0.988
First TNF inhibitor use, n (%)	30 (88.2%)	92 (92.0%)	0.507	3 (9.7%)	4 (7.7%)	0.753
Initial BASDAI score, mean (SD)	6.9 (1.6)	6.9 (1.5)	0.905	6.9 (1.6)	7.0 (1.6)	0.811
HLA-B27, n (%)	30 (90.9%)	84 (90.3%)	0.841	29 (93.5%)	49 (94.2%)	0.899
ESR, mean (SD), mm	40.3 (30.3)	41.3 (29.1)	0.863	39.2 (31.1)	45.7 (32.3)	0.378
CRP ≥ 0.5 mg/dL, n (%)	26 (76.5%)	79 (79.0%)	0.757	23 (74.2%)	42 (78.8%)	0.623
Time to achieving clinical remission, mean (SD), in weeks	15.3 (12.4)	16.1 (14.4)	0.318	15.7 (13.0)	13.6 (6.9)	0.411
Time to tapering dose, median (IQR), in weeks	NA	19.5 (10.1-39,6)	NA	NA	24.3 (6.0-35.1)	NA
NSAID, n (%)	32 (94.1%)	95 (95.0%)	0.842	30 (96.8%)	49 (94.2%)	0.601
Sulfasalazine, n (%)	18 (52.9%)	55 (55.0%)	0.835	17 (54.8%)	28 (53.8%)	0.930
MTX, n (%)	11 (32.4%)	24 (24.0%)	0.338	10 (32.3%)	15 (28.8%)	0.743
Low-dose steroid, n (%)	7 (20.6%)	27 (27.0%)	0.458	1 (3.2%)	4 (7.7%)	0.646
MPR of NSAID or DMARD, mean (SD), %*	92.7 (6.2)	91.8 (5.2)	0.491	93.0 (6.4)	91.6 (5.2)	0.321

BASDAI: Bath Ankylosing Spondylitis Activity Index; CRP: C-reactive protein; DMARD: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; IQR: interquartile range; MPR: medication possession ratio; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drug; SD: Standard deviation; TNF-α: tumour necrosis factor-alpha. *MPR of DMARDs was calculated in patients who did not use NSAIDs at baseline.

analysis (adjusted HR 10.447, 95% CI 2.513–43.433, p=0.001). Female gender was also related to a shorter drug survival for the low-dose regimen, but it was not significant in multivariate analysis (adjusted HR 2.982, 95% CI 0.948–9.382, p=0.062) (Table III).

Sensitivity analysis

Although the dose reduction strategy was relatively homogeneous, there were some 'outliers' regarding the first standard-dose period in the low-dose group. We performed two sensitivity analyses, one excluding nine patients who tapered the dose after more than 1 year of standard-dose and another excluding four patients as outliers regarding the proportion of the low-dose period in total duration of etanercept treatment. None of which did alter the result of original survival analysis.

In addition, to exclude the possibility that patients with a more favourable safety profile during the remission induction were assigned to the low-dose group, incidence rates of adverse events during the first year of treatment were calculated for the two groups (Supplementary Table I). There were no differences in the occurrence of any adverse events between the two groups.

Discussion

The results of the present study showed that low-dose etanercept treatment in AS patients who achieved clinical remission had a comparable drug survival to a standard-dose regimen during a long-term observation period. In addition, both regimens similarly inhibited disease activity, and the incidence of some adverse events appeared to be decreased in the low-dose group, especially injection site reactions. Taken together, these finding suggest that low-dose etanercept treatment for 'maintenance' of clinical remission has favourable efficacy and safety as com-

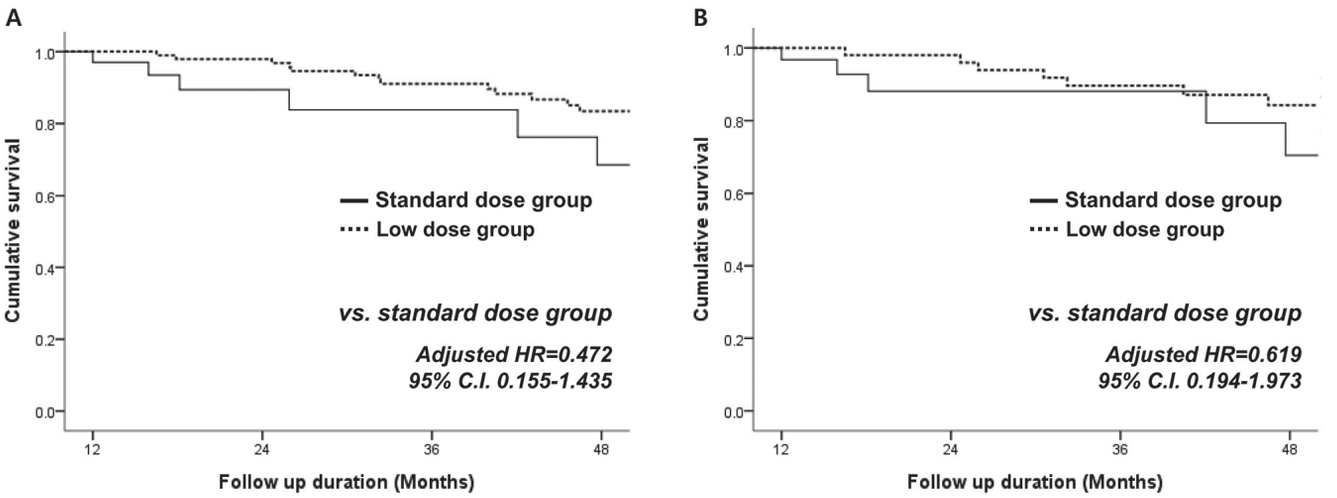

Fig. 3. Kaplan-Meier curve of drug survival between standard and low dose groups in a whole population (**A**) and propensity-score matched population (**B**).

Table II. Incidence rates of adverse events.

	Low-dose group	Standard-dose group	Incidence rate ratio (Low/Standard)	*p*-value
Any AE	54.2 (47.6-61.5)	61.5 (46.9-79.4)	0.884 (0.665-1.176)	0.397
Uveitis	12.5 (9.4-16.2)	9.4 (4.3-17.8)	1.334 (0.659-2.699)	0.423
Infection	21.0 (17.0-25.8)	17.7 (10.3-28,4)	1.194 (0.712-2.002)	0.501
Injection site reaction	2.7 (1.4-4.8)	8.3 (3.6-16.4)	0.327 (0.134-0.801)	0.014
Headache	2.9 (1.6-5.0)	6.3 (2.3-13.6)	0.473 (0.180-1.244)	0.129
Gastroenteritis	5.2 (3.3-7.8)	3.1 (0.6-9.1)	1.673 (0.502-5.573)	0.402
Other*	9.5 (6.9-12.9)	13.6 (7.2-23.1)	0.705 (0.379-1.314)	0.271
Any CSAE	4.1 (2.4-6.5)	5.2 (1.7-12.2)	0.783 (0.291-2.108)	0.628
Uveitis	2.3 (1.1-4.2)	3.1 (0.6-9.1)	0.725 (0.199-2.633)	0.625
Infection	0.5 (0.0-1.6)	1.0 (0.0-5.8)	0.435 (0.039-4.795)	0.497
Injection site reaction	0.7 (0.1-2.0)	1.0 (0.0-5.8)	0.652 (0.068-6.270)	0.711
Malignancy	0.2 (0.0-1.3)	0	NA	NA

AE: adverse event; CSAE: clinically significant adverse event. Incidence rate (95% confidence interval) is expressed per 100 person-years.
*Includes skin rash, nephrolithiasis, tingling sense in extremities, gallstones and leukopenia.

Table III. Clinical factors affecting drug survival of low-dose etanercept regimen.

	Univariate analysis		Multivariate analysis†	
	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Female gender	2.856 (1.186-6.874)	0.019	2.982 (0.948-9.382)	0.062
Age	1.005 (0.974-1.037)	0.768	1.001 (0.968-1.035)	0.958
Disease duration	0.999 (0.920-1.084)	0.974	1.052 (0.972-1.139)	0.209
Previous TNF inhibitor use	12.429 (3.092-49.961)	<0.001	10.447 (2.513-43.433)	0.001
Initial BASDAI score	0.965 (0.721-1.291)	0.810	0.842 (0.585-1.212)	0.354
Time to dose reduction >24 weeks	0.250 (0.083-0.756)	0.014	0.261 (0.084-0.809)	0.020
HLA-B27	0.804 (0.186-3.472)	0.770	*	
ESR	1.010 (0.995-1.025)	0.203	*	
CRP	0.999 (0.882-1.132)	0.990	*	
Baseline medication				
MTX	1.441 (0.587-3.539)	0.426	1.934 (0.766-4.882)	0.163
Low-dose steroid	0.592 (0.200-1.753)	0.344	*	

BASDAI: Bath Ankylosing Spondylitis Activity Index; CI: confidence interval; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HR: hazard ratio; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drug; TNF: tumour necrosis factor.
†Multivariate analysis is adjusted by age, gender, disease duration, initial BASDAI score, baseline MTX and clinical factors with *p*-value <0.2 in univariate analysis.
*Excluded from multivariate analysis because *p*-value >0.2 in univariate analysis.

pared with standard-dose treatment in the real world.

Previous studies have shown that discontinuation of TNF inhibitors in well-controlled AS patients lead to clinical relapse within a few weeks to months (7, 21). However, continuous use leads to significant financial burden and possibly increases the risk of adverse events. Therefore, low-dose etanercept seems to be ideal with regard to cost/efficacy ratio and safety (22). Lee *et al*. first reported 16 cases where 25 mg/week of etanercept was effective in maintaining clinical remission after 12 weeks of standard-dose treatment (10). In another retrospective analysis, progressive increases in the dosing interval of etanercept did not increase disease activity and showed high drug retention rate (14). However, these studies did not have a control group, making direct comparison impossible. Recently, Závada *et al*. showed that tailored dose reduction of TNF inhibitors after achieving low disease activity (BASDAI <4) produced similar clinical efficacy at 1 year as propensity-score matched controls with standard-dose treatment (23). This is in agreement with our results, but we further demonstrated continued efficacy and safety of low-dose etanercept treatment for up to 4 years. If maintenance of the treatment goal can be continued with a reduced dose, it may also provide a huge cost benefit to patients and health care systems.

It is rather interesting that drug survival of the low-dose group was numerically

higher than in the standard-dose group. In the whole study population, patients in the standard-dose group tended to have longer disease durations, be older and more likely to be women, which are unfavourable factors in the treatment of AS. The difference in drug survival between the two groups was decreased in the propensity-score matched population but persisted. This was partly because we excluded patients whose drug survival was less than 12 months. Previous reports suggested that discontinuation of etanercept due to inefficacy occurs most frequently during the first year of treatment, whereas withdrawal due to adverse events occurs at a relatively constant rate (24, 25). In fact, there were only seven cases of inefficacy during the observation period and CSAEs arose more frequently in this study. Therefore, the numerically superior drug survival in the low-dose group may be a reflection of its marginally favourable safety.

Although the number of reports on low-dose etanercept treatment in AS is increasing, there is no consensus as to a dosing schedule that provides maximum efficacy. Therapeutic effects of TNF inhibitors are rapid, so AS patients who are responsive to treatment usually achieve clinical remission within several weeks. However, most patients who start TNF inhibitors at a low-dose fail to achieve clinical remission and eventually escalate the dose (26, 27). Therefore, determining proper duration of standard-dose treatment before tapering is essential for a universal recommendation. In this respect, it is of note that dose reduction after at least 24 weeks of standard treatment was significantly associated with a longer drug survival in this study. Previous pharmacokinetic studies suggested that trough levels of etanercept gradually increase toward steady-state during the first 24 weeks of treatment and are proportional to the dose (28, 29). Therefore, premature dose reduction during this period may result in insufficient concentrations of the drug. Although an exact therapeutic window remains uncertain, a recent study demonstrated that low etanercept levels at 24 weeks of treatment was significantly associated with high disease activity and inflammatory markers (30). The above results indicate that an adequate standard-dose period prior to de-escalation may be a more appropriate strategy in low-dose etanercept treatment.

By contrast, patients previously treated with other TNF inhibitors showed a shorter drug survival than first users in a subgroup analysis of the low-dose group. AS patients switching TNF inhibitors usually show a decreased response rate and drug survival (4, 31). However, few studies have investigated the impact of low-dose etanercept in these patients. We could not compare drug survival of switchers between groups because their numbers were too small. It needs to be clarified in future studies whether a tapering regimen shows a comparable efficacy to standard-dose treatment in AS patients who switched from other TNF inhibitors.

This study has some limitations that need to be considered. First, it is a non-randomised, observational study, and there was a significant difference in patient age between groups. Comparable drug survival in the low-dose group was not changed in the propensity score-matched population, so it is less likely that a disparity in age severely biased the results in our study. However, despite this rigorous adjustment to minimise the imbalance of pre-treatment characteristics, complete removal of bias from unmeasured confounders is impossible by statistical techniques. For example, although tapering was considered in patients with clinical remission, it was decided by four different physicians. We cannot exclude the possibility that each physician's decision on selecting patients for a decreased dose could be different. Second, although the BASDAI was used for monitoring disease activity, other methods, such as the Ankylosing Spondylitis Disease Activity Score (ASDAS), BASMI or radiologic progression, were not uniformly assessed. However, BASDAI is well-established and valid indicator of disease activity. We also considered CRP in assessing clinical remission and responsiveness of treatment to make up for any weaknesses of the BASDAI. In addition, since there is no universal criteria for remission, the definition of clinical remission used in this study could be different, which makes comparison of the results to other studies difficult. Finally, drug survivals of both groups were higher than previously reported (4, 24). Although we analysed only patients with sustained clinical response to etanercept, it is possible that censored patients with low compliance might have overestimated drug survival.

In conclusion, the results from this study indicate that low-dose etanercept for the maintenance of clinical remission in AS can be an alternative treatment option in terms of its comparable long-term efficacy and favourable safety. Although an optimal schedule of this 'step-down' strategy is still unclear, at least 24 weeks of standard-dose prior to tapering appears to be beneficial to successful outcome of low-dose etanercept treatment.

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References

1. CALIN A, DIJKMANS BA, EMERY P *et al*.: Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. *Ann Rheum Dis* 2004; 63: 1594-600.
2. DAVIS JC, JR., VAN DER HEIJDE DM, BRAUN J *et al*.: Efficacy and safety of up to 192 weeks of etanercept therapy in patients with ankylosing spondylitis. *Ann Rheum Dis* 2008; 67: 346-52.
3. HEIBERG MS, KOLDINGSNES W, MIKKELSEN K *et al*.: The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. *Arthritis Rheum* 2008; 59: 234-40.
4. GLINTBORG B, OSTERGAARD M, KROGH NS, DREYER L, KRISTENSEN HL, HETLAND ML: Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. *Ann Rheum Dis* 2010; 69: 2002-8.
5. BRAUN J, BARALIAKOS X, LISTING J *et al*.: Persistent clinical efficacy and safety of anti-tumour necrosis factor alpha therapy with infliximab in patients with ankylosing spondylitis over 5 years: evidence for different types of response. *Ann Rheum Dis* 2008; 67: 340-5.
6. VAN DER HEIJDE D, LANDEWÉ R, EINSTEIN S

et al.: Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. *Arthritis Rheum* 2008; 58: 1324-31.

7. BRANDT J, KHARIOUZOV A, LISTING J *et al*.: Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum* 2003; 48: 1667-75.
8. ARA RM, REYNOLDS AV, CONWAY P: The cost-effectiveness of etanercept in patients with severe ankylosing spondylitis in the UK. *Rheumatology* (Oxford) 2007; 46: 1338-44.
9. SCHABERT VF, WATSON C, JOSEPH GJ, IVERSEN P, BURUDPAKDEE C, HARRISON DJ: Costs of tumor necrosis factor blockers per treated patient using real-world drug data in a managed care population. *J Manag Care Pharm* 2013; 19: 621-30.
10. 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.
11. NAVARRO-COMPAN V, MOREIRA V, ARIZA-ARIZA R, HERNANDEZ-CRUZ B, VARGAS-LEBRON 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.
12. 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.
13. PACCOU J, BACLE-BOUTRY MA, SOLAU-GERVAIS E, BELE-PHILIPPE P, FLIPO RM: Dosage adjustment of anti-tumor necrosis factor-alpha inhibitor in ankylosing spondylitis is effective in maintaining remission in clinical practice. *J Rheumatol* 2012; 39: 1418-23.
14. LEE J, NOH JW, HWANG JW *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.
15. KAYMAKCALAN Z, SAKORAFAS P, BOSE S *et al*.: Comparisons of affinities, avidities, and complement activation of adalimumab, infliximab, and etanercept in binding to soluble and membrane tumor necrosis factor. *Clin Immunol* 2009; 131: 308-16.
16. GARCES S, DEMENGEOT J, BENITO-GARCIA E: The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. *Ann Rheum Dis* 2013; 72: 1947-55.
17. CHEN DY, CHEN YM, TSAI WC *et al*.: Significant associations of antidrug antibody levels with serum drug trough levels and therapeutic response of adalimumab and etanercept treatment in rheumatoid arthritis. *Ann Rheum Dis* 2015; 74: e16.
18. 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.
19. VAN DER HEIJDE D, SIEPER J, MAKSYMOWYCH WP *et al*.: 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis* 2011; 70: 905-8.
20. SCIRE CA, CAPORALI R, SARZI-PUTTINI P *et al*.: Drug survival of the first course of anti-TNF agents in patients with rheumatoid arthritis and seronegative spondyloarthritis: analysis from the MonitorNet database. *Clin Exp Rheumatol* 2013; 31: 857-63.
21. BARALIAKOS X, LISTING J, BRANDT J *et al*.: Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. *Arthritis Res Ther* 2005; 7: R439-44.
22. BERTHELOT JM: Efficacy of low-dose etanercept (25 mg/week): how much do we know? *Joint Bone Spine* 2012; 79: 335-7.
23. ZAVADA J, UHER M, SISOL K *et al*.: A tailored approach to reduce dose of anti-TNF drugs may be equally effective, but substantially less costly than standard dosing in patients with ankylosing spondylitis over 1 year: a propensity score-matched cohort study. *Ann Rheum Dis* 2016; 75: 96-102.
24. DUCLOS M, GOSSEC L, RUYSSEN-WITRAND A *et al*.: Retention rates of tumor necrosis factor blockers in daily practice in 770 rheumatic patients. *J Rheumatol* 2006; 33: 2433-8.
25. FRAZIER-MIRONER A, DOUGADOS M, MARIETTE X *et al*.: Retention rates of adalimumab, etanercept and infliximab as first and second-line biotherapy in patients with rheumatoid arthritis in daily practice. *Joint Bone Spine* 2014; 81: 352-9.
26. INMAN RD, MAKSYMOWYCH WP: A double-blind, placebo-controlled trial of low dose infliximab in ankylosing spondylitis. *J Rheumatol* 2010; 37: 1203-10.
27. SIDIROPOULOS P, KRITIKOS HD, SIAKKA P *et al*.: Low dose of infliximab is inadequate in most patients with spondylarthropathies. *Clin Exp Rheumatol* 2005; 23: 513-6.
28. ZHOU H: Clinical pharmacokinetics of etanercept: a fully humanized soluble recombinant tumor necrosis factor receptor fusion protein. *J Clin Pharmacol* 2005; 45: 490-7.
29. LEE H, KIMKO HC, ROGGE M, WANG D, NESTOROV I, PECK CC: Population pharmacokinetic and pharmacodynamic modeling of etanercept using logistic regression analysis. *Clin Pharmacol Ther* 2003; 73: 348-65.
30. KNEEPKENS EL, KRIECKAERT CL, VAN DER KLEIJ D *et al*.: Lower etanercept levels are associated with high disease activity in ankylosing spondylitis patients at 24 weeks of follow-up. *Ann Rheum Dis* 2014.
31. LIE E, VAN DER HEIJDE D, UHLIG T *et al*.: Effectiveness of switching between TNF inhibitors in ankylosing spondylitis: data from the NOR-DMARD register. *Ann Rheum Dis* 2011; 70: 157-63.