Efficiency of dose reduction strategy of etanercept in patients with axial spondyloarthritis

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Abstract

Objective

To evaluate the efficacy of different tapering or discontinuation strategies of etanercept in a cohort of axial spondyloarthritis from South China.

Methods

We performed a retrospective cohort study. Axial SpA patients who achieved clinical remission for at least 6 months after receiving a standard dose of etanercept therapy were enrolled. Different tapering or discontinuation strategies were compared.

Results

Altogether, 258 cases were enrolled. No differences were found in baseline characteristics among the three groups. Significantly more patients on discontinuation group (19%) than tapering group (5.4%, p<0.001) relapsed as early as 6 months. Almost all of the patients (103/107, 96.3%) in taper 25% group and more than 80% (71/88, 80.7%) of the patients in taper 50% group maintained low disease activity (LDA) or clinical remission during the first year. At the end of the 2-year follow-up, the percentage of patients maintaining LDA or remission were 28.6% (discontinuation), 55.7% (taper 50%), 84.1% (taper 25%), respectively. Activity indexes were significantly lower in taper 25% group compared to the other two groups. Patients in discontinuation group and tapering 50% group, with longer SpA duration were more likely to relapse, and remission>12 months before discontinuation/tapering helped to reduce relapse.

Conclusion

It is feasible to slowly increase the dosing interval and transit to the lowest effective dosing interval for some patients in remission/LDA. Prolonging the time under remission before tapering help to improve the outcome. Tapering 25% of the etanercept dose every 3 months may be a pragmatic approach for more cost-effective use of the drug.

Key words

axial spondyloarthritis, etanercept, tapering, discontinuation, cost-effectiveness

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Introduction

TNF inhibitors have deeply changed the management of axial spondyloarthritis (axSpA). axSpA includes patients with AS and patients with non-radiographic axSpA (nr-axSpA). As the effective therapeutic alternatives to non-steroidal anti-inflammatory drugs for axSpA, TNF-α inhibitors improve physical function and decrease disease activity. Remission or low disease activity (LDA) is now a realistic goal for its excellent efficacy (1, 2). Despite the benefits of TNF inhibitors, patients need to stay on this treatment for a long time. There has been a clear medical need to consider the long-term safety and increased drug costs (3, 4). It was reported that the mean direct costs on SpA were €2640 per patient/year in the Netherlands, with 13% of the costs related to drug expenditure (5). Unanswered question for physicians is whether tumour necrosis factor inhibitors can be reduced or even stopped, or how can it be reduced in patients have achieved remission or LDA. There is still little information to TNF inhibitors tapering in AS. Such data are critical for clinical practice and economic analyses. The current study aimed to investigate the effectiveness and safety of discontinuation or tapering strategies of anti-TNF therapy. We observed one of the TNF inhibitors, etanercept, to evaluate if the tapering or discontinuation would still maintain remission or LDA. We sought to better discriminate the patients eligible to undergo TNF blocker reduction or discontinuation, and try to find a way in balancing the quality of the patients' lives, the side effects and the cost-effectiveness.

Methods

We performed a retrospective cohort study using data obtained from the first affiliated hospital of Sun Yat-sen University, Guangzhou, China, between January 2012 and December 2014. axSpA was defined based on the ASAS classification criteria. Non-radiographic axSpA (nr-axSpA) was characterised by a lack of definitive radiographic sacroiliitis.

From January 2012 to December 2014, axial SpA patients who achieved clinical remission (defined as Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] <2 and normal CRP or Ankylosing Spondylitis Disease Activity Score [ASDAS] <1.3) for at least 6 months after receiving a standard dose of etanercept (the bio-original) therapy were identified (6).

Etanercept was discontinued (without the procedure of tapering) or tapered. The patients were tapered on etanercept by increasing the interval between drug administrations. For the tapering cases, the protocol of tapering 25% was to space by 25% every 3 months (from every 7 days per injection to every 9 days per injection for the first time of spacing, then spaced more gradually) up to complete stop and the protocol of tapering 50% was to space by 50% every 3 months (from every 7 days per injection to every 14 days per injection for the first time of spacing, then spaced more gradually) up to complete stop. After 3 months from biologic tapering, patients who were still at LDA or remission were tapered again. With the frequency of injection spaced out gradually, the dosage of each injection was still 50 mg. Patients were assessed at the baseline and every 3 months thereafter for 2 years.

The following treatment after discontinuation of etanercept was non-steroidal anti-inflammatory drugs (NSAIDs), and sulfasalazine if necessary, on standard dose.

The percentage of patients maintaining LDA (BASDAI <4) or remission (BASDAI <2 and normal CRP or ASDAS <1.3) after etanercept reduction or discontinuation, the relapse rate and change on disease activity parameters were recorded (relapse defined as BASDAI ≥4 or an increase in BASDAI of ≥2 units). Four ASDAS categories were defined: inactive disease (ASDAS <1.3), moderate disease activity (ASDAS ≥1.3 and <2.1), high disease activity (ASDAS ≥2.1 and ≤3.5) and very high disease activity (ASDAS >3.5) (7, 8).

Demographic, clinical, and radiological data were recorded for all the enrolled patients. MRI of sacroiliac joints was performed at baseline, 12 months, and 24 months.

Symptoms were evaluated on VAS (verbally administered 0–10 numerical rat-

ing scale, with 0 indicating the absence and 10 an extremely severe symptom).
The disease activity and physical functioning were measured with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Disease Activity Score (ASDAS), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) (8-11).
Spinal mobility was measured by Bath Ankylosing Spondylitis Metrology Index (BASMI score of 0–10) (12).
The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the first affiliated hospital of Sun Yat-sen University, Guangzhou, China (project identification code: [2017]053).
Informed consent was obtained from the participants for the study and publication of any accompanying data.

Statistical analysis

Data are expressed as means and standard deviation, percentages and median and interquartile range (IQR) (P25–P75). Changes from baseline were measured with Wilcoxon signed-rank test, continuous variables were measured with *t*-test and nominal variables was measured with Chi-square test to calculate the differences between the different treatment methods. Kaplan-Meier analysis and cox regression were used to analyse the differences of relapse and significance of clinical variables. *P*-values <0.05 were considered statistically significant. The analyses were performed using IBM SPSS 20.0 software.

Results

Baseline characteristics

From January 2012 to December 2014, 258 cases of axial SpA patients who achieved clinical remission for at least 6 months after receiving a standard dose of etanercept (50mg/w) therapy were identified. Etanercept was discontinued in 63 cases. For the tapering cases, injections of 107 cases spaced by 25% every 3 months up to complete stop and 88 cases spaced by 50% every 3 months up to complete stop. Baseline characteristics of the patients are summarised in Table I. No differences were found in any of the baseline characteristics.

Table I. Baseline characteristics of the patients.

	Discontinuation (n=63)	Tapering 25% (n=107)	Tapering 50% (n=88)	*p*-value
Age, years	32.3 ± 11.6	35.7 ± 12.4	30.9 ± 18.5	NS
male, n %	55 (87.3)	98 (91.6)	78 (88.6)	NS
Disease duration, years	5.2 ± 3.7	7.1 ± 5.4	6.6 ± 4.3	NS
HLA-B27 positive, n %	60 (95.2)	102 (95.3)	81 (92.0)	NS
nr-axSpA, n %	15 (23.8)	30 (28.0)	16 (18.1)	NS
ESR, mm/h	9.3 ± 5.2	11.4 ± 5.4	10.9 ± 4.9	NS
CRP, mg/dL	1.4 ± 0.8	2.0 ± 1.2	2.1 ± 1.1	NS
Patients with elevated ESR, n %	1	2	0	NS
Patients with elevated CRP, n %	0	1	0	NS
NRS for Back pain, 0-10	1.0 ± 0.9	1.2 ± 0.8	0.6 ± 1.0	NS
BASDAI, 0-10	1.3 ± 0.4	1.2 ± 0.8	1.1 ± 0.7	NS
BASFI, 0-10	1.2 ± 0.5	1.6 ± 0.9	1.4 ± 0.6	NS
BASMI, 0-10	1.1 ± 0.4	1.2 ± 0.6	1.0 ± 0.5	NS
ASDAS-CRP	0.9 ± 0.3	1.2 ± 0.4	1.0 ± 0.2	NS
Active inflammatory lesions of the SIJs on MRI, n%	2 (3.2)	3 (2.8)	1 (1.1)	NS
Remission time before discontinuation or tapering, months	7.3 ± 2.6	7.6 ± 2.9	8.0 ± 2.8	NS

Values are given as mean (S.D.) unless otherwise indicated. nr-axSpA: non-radiographic axial spondyloarthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NRS: numerical rating scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Function Index; BASMI: BASMI, Bath Ankylosing Spondylitis Metrology Index; ASDAS: ankylosing spondylitis disease activity score; NS: not significant.

Discontinuation or tapering of etanercept

• *Clinical treatment response during the first year*

Patients who relapsed as early as 6 months had significantly more patients on discontinuation group (19%) than the tapering group (5.4%, $p<0.001$), and about one-third (20/63, 31.7%) of the patients relapsed in discontinuation group at the end of first year (Fig. 1A). At 12 months, patients who relapsed had the highest BASDAI and ASDAS-CRP score in discontinuation group compared to the other two groups, and the scores were higher in taper 50% group than in taper 25% group. Furthermore, mean CRP and ESR remained normal in taper 25% group (not significant compared to baseline) and remained low in taper 50% group, but not so promising in discontinuation group. Almost all of the patients (103/107, 96.3%) in taper 25% group and more than 80% (71/88, 80.7%) of the patients in taper 50% group maintained LDA or clinical remission during the first year. Many more patients in discontinuation group (52/63%, 92.1%) were treated with concomitant NSAID than in taper group (taper 25%: 55/107, 51.4%; taper 50%: 63/88, 71.2%). The clinical and laboratory results are presented in Table II.

• *Clinical treatment response at the end of 2 years*

At the end of the 2-year follow-up, 45 cases in discontinuation group (71.4%) relapsed, 17 cases (15.9%) in taper 25% group relapsed (median=427 days (IQR 286–688)), and 39 cases (44.3%) in taper 50% group relapsed (median=306 days (IQR 214–461)) (Fig. 1A). The percentage of patients maintaining LDA or remission after discontinuation or tapering of the anti-TNF at the end of the study were 28.6% (discontinuation), 55.7% (taper 50%), 84.1% (taper 25%), respectively. More patients were treated with concomitant NSAID than the first year (discontinuation: 100%; taper 25%: 62.6%; taper 50%: 84.1%). Mean NRS back pain score, mean ESR, mean CRP, mean BASDAI score, mean BASFI score, mean BASMI score and mean ASDAS-CRP score remained low in taper 25% group. As compared to the discontinuation group and taper 50% group, these scores were significantly lower, though some of them did increase compared to the baseline. The

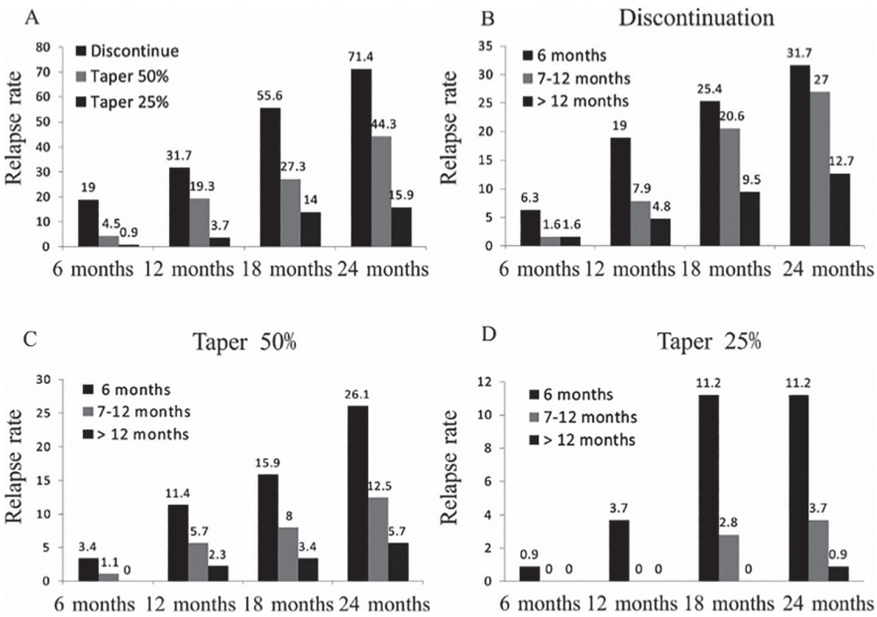

Fig. 1. Relapse rate during the observation. **A**: Different relapse rate of the discontinuation group, taper 50% group and taper 25% group. **B**: Different relapse rate -12 months or of discontinuation group when the patients were on remission>12 months, 76 months before discontinuation. **C**: Different relapse rate of taper 50% group when the patients were on remission>12 months, 7–12 months or 6 months before tapering. **D**: Different relapse rate of taper 25% group when the patients were on remission >12 months, 7–12 months or 6 months before tapering.

Table II. Clinical and laboratory characteristics of patients at 12 months.

	Discontinuation	Tapering 25%	Tapering 50%	*p*-value
ESR, mm/h	30.2 ± 27.4*	13.2 ± 8.5	22.1 ± 18.6*	*<0.001
CRP, mg/dL	10.3 ± 13.4*	2.2 ± 1.7	5.5 ± 7.0*	*<0.001
Patients with elevated ESR, n %	22 (34.5)*	3 (2.8)	19 (21.6)*	*<0.001
Patients with elevated CRP, n %	21 (33.3)*	4 (3.7)	17 (19.3)*	*<0.001
NRS for Back pain, 0-10	2.6 ± 1.3*	1.5 ± 0.8	1.2 ± 1.0*	*<0.001
BASDAI, 0-10	3.0 ± 1.9*	1.4 ± 0.9	1.2 ± 0.8	*<0.001
BASFI, 0-10	1.3 ± 1.0	1.5 ± 0.9	1.5 ± 1.3	NS
BASMI, 0-10	1.2 ± 0.6	1.1 ± 0.6	1.1 ± 0.9	NS
ASDAS-CRP	1.5 ± 0.9*	1.1 ± 0.3	1.2 ± 0.7*	*<0.001
Active inflammatory lesions of the SIJs on MRI, n %	25 (39.7)*	4 (3.7)	22 (25)*	*<0.001
Concomitant NSAID use, n%	58 (92.1)#	55 (51.4)#	63 (71.2)#	#<0.01

*Comparisons to baseline values; #compared between groups; NS: not significant

clinical and laboratory results are presented in Table III.

During the course of observation, patients had much less relapse when they were on standard dose of etanercept to keep remission >12 months than those on standard dose of etanercept to keep remission for 6 months before discontinuation or tapering. At 12 months after discontinuation/tapering, the proportion of relapse rate in discontinuation group, taper 50% group and taper 25% group were 4.8% (>12 months) *vs*. 19% (6 months) (Fig. 1B), 2.3% (>12 months) *vs*. 11.4% (6 months) (Fig. 1C), 0% *vs*. 3.7% (Fig. 1D), respectively. But no significance was found. At the end of observation (24 months), the proportion of relapse rate in discontinuation group, taper 50% group and taper 25% group were 12.7% (>12 months) *vs*. 31.7% (6 months) ($p<0.05$) (Fig. 1B), 5.7% (>12 months) *vs*. 26.1% (6 months) ($p<0.05$) (Fig. 1C), 0.9% (>12 months) *vs*. 11.2% (6 months) ($p<0.05$), respectively (Fig. 1D).

Kaplan-Meier analysis demonstrated that patients on different discontinuation/tapering strategies had different outcomes. Time-dependent relapse was significantly associated with treatment strategies ($p<0.001$). Time from relapse to discontinuation/tapering was shorter in discontinuation group (mean, 15.63 months) than in taper 50% group (mean, 19.94 months) and taper 25% group (mean, 22.67 months). (Fig. 2)

On multivariable cox regression analysis, discontinuation/tapering strategies and duration of remission were independently associated with relapse. Multivariate analysis shown that discontinuation (HR: 9.350, 95% CI=5.195–16.830, $p<0.001$), taper 50% (HR: 3.232, 95% CI=1.823–5.729, $p<0.001$), SpA duration (HR: 1.052, 95% CI=1.006-1.100, $p=0.027$), and duration of remission (HR: 0.878, 95% CI=0.797–0.968, $p=0.009$) were independent prognostic factors, which suggested that patients in discontinuation group and tapering 50% group, with longer SpA duration were more likely to relapse than patients in tapering 25% group, and longer duration of remission helped to reduce relapse. The factors not significant on multivariate cox regression included age, disease activity at the start of etanercept, clinical response in the first 6 months, sex, B27 status, CRP level at the time of discontinuation / tapering, etc. (Table IV)

Altogether there were 61 cases of nr-axSpA. As shown in Table V, the baseline characteristics of them were similar to the radiographic axSpA patients, except that disease duration before admission to hospital was a little bit shorter in nr-axSpA than in radiological axSpA. Most of the relapse rates in discontinuation, taper 25% and taper 50% group at different time points (6 months, 12 months, 18 months, 24 months) were slightly lower in nr-axSpA than in radiographic axSpA, except that the relapse rates of 6 months and 12 months in discontinuation group were slightly higher in nr-axSpA than in radiographic axSpA (No statistical significance was found). Same trend of relapse rate was found in nr-axSpA and radiographic axSpA. Patients had much less relapse when they were on remission >12 months than those on remission for 6 months before discontinuation or tapering.

Side effects

Etanercept was well tolerated in all patients. Histories of virus hepatitis were documented in 23 cases before treatment, and all of them maintained stable

Table III. Clinical and laboratory characteristics of patients at 2 years.

	Discontinuation	Tapering 25%	Tapering 50%	*p*-value
ESR, mm/h	43.9 ± 31.5**	12.0 ± 12.7	29.6 ± 22.3**	**<0.001
CRP, mg/dL	12.5 ± 9.7**	3.1 ± 1.7*	5.5 ± 7.0**	**<0.001 *<0.05
Patients with elevated ESR, n %	46 (73.0)**	18 (16.8)**	41 (46.6)**	**<0.001
Patients with elevated CRP, n %	48 (76.2)**	17 (15.9)**	42 (47.7)**	**<0.001
NRS for Back pain, 0-10	4.3 ± 3.6**	1.1 ± 1.2	3.5 ± 2.4**	**<0.001
BASDAI, 0-10	4.3 ± 2.1**	1.3 ± 1.1	3.3 ± 2.0**	**<0.001
BASFI, 0-10	2.9 ± 1.8**	1.4 ± 1.2	1.9 ± 1.7*	**<0.001 *<0.05
BASMI, 0-10	2.1 ± 1.7**	1.1 ± 0.7	1.4 ± 1.1**	**<0.001
ASDAS-CRP	2.1 ± 0.9**	1.2 ± 0.6*	1.5 ± 0.9**	**<0.001 *<0.05
Active inflammatory lesions of the SIJs on MRI, n %	49 (77.8)**	12 (11.2)*	36 (40.9)**	**<0.001 *<0.05
Concomitant NSAID use, n%	63 (100)#	67 (62.6)#	74 (84.1)#	#<0.001

*Comparisons to baseline values; #compared between groups; NS: not significant.

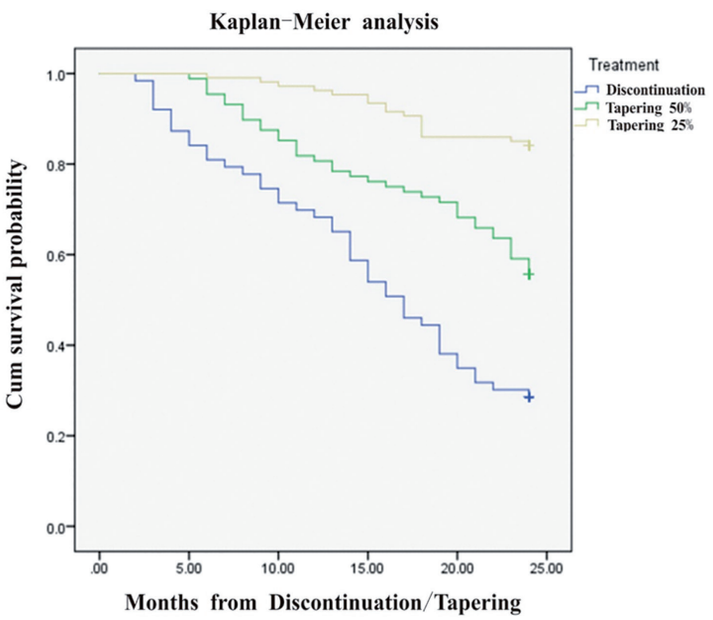

Fig. 2. Kaplan-Meier analysis for time to discontinuation/tapering. The time interval from relapse to discontinuation/tapering of etanercept was calculated using the Kaplan-Meier method. Patients in discontinuation group experienced shorter relapse time than patients in tapering 50% group and tapering 25% group, patients in tapering 50% group experienced shorter relapse time than patients in tapering 25% group.

during the follow-up. No case of tuberculosis or severe infection was observed. Minor side effects included localised rash at the site of rejection, a less than 2-fold increase in aminotransferase and slight dizziness, all of which were transient and did not interrupt the treatment.

Discussion

In this study, we observed the effectiveness of different extended dosing strategies of etanercept in axSpA patients for two years. All the patients achieved clinical remission for at least 6 months after receiving a standard dose of etanercept therapy. TNF inhibitors were well tolerated in general. Considering the high prevalence of tuberculosis and virus hepatitis in China (13-15), etanercept is preferable for possible safety issues.

Etanercept has been proved to be effective in reducing the axial and peripheral symptoms of AS and improving patient quality of life (QOL) (16). Given the cost of TNF inhibitors, they may be considered unaffordable by some patients or would sometimes lead to discontinuation despite the risk of recurrence, especially when in China, most patients do not have enough insurance to cover the costs of anti-TNF therapy. Reducing possible adverse effects by cutting the dosage and especially, saving costs, is critical for the drug survival and better outcome. Most of the time, the patients chose to discontinue or reduce the dose since they had no other choice due to economic issues, even in some cases discontinuation or dose reduction was not recommended. In this study, we collected the data of patients who could not afford to pay for full dose etanercept all the time and chose to discontinue or reduce the dose after remission for at least 6 months, and made a comparison among discontinuation and different reduction strategies.

There is published evidence concerning the use of discontinuation or tapering strategies of anti-TNF therapy in axSpA patients after achieving clinical remission or LDA with a standard dose (6, 17, 18). As for the efficacy of etanercept discontinuation strategy for maintaining LDA or remission in patients with axSpA after achieving remission with a standard dose, Brandt *et al*. (19) conducted an observational research after participation in an RCT, and Deng *et al*. (20) conducted a RCT to evaluate the effect of thalidomide to prevent flare after discontinuation. Follow up time of the above researches were both within one year. Brandt *et al*. claimed that 100% of the patients relapsed at 36 weeks, and Deng *et al*. claimed that more than 70% of the patients relapsed at 52 weeks.

We found that 31.7% of the patients relapsed in the discontinuation group at 52 weeks. Though not very promising, the relapse rate in the present study was much lower than the researches mentioned above. Time on etanercept after achieving remission before discontinuation was longer in our research (6 months *vs*. 3 months and 2.5 months), that may be the reason of lower relapse rate in the first year, which suggested that long remission may help to reduce relapse.

After discontinuation of etanercept, the patients were on NSAIDs and sulfasalazine if necessary, because they could not afford biological agents. Still, considerable amount of patients relapsed within 2 years of observation. For the relapsed patients, doctors would not recommend discontinuation of biological agents, however, poor economic situations re-

Table IV. Associated factors of relapse after discontinuation/tapering of etanercept.

	Hazard ratio	95%CI	*p*-value
Age (yr)	1.012	0.984-1.041	0.410
SpA duration (month)	1.052	1.006-1.100	0.027*
Disease activity at the start of etanercept	0.897	0.700-1.151	0.393
Clinical response in the first 6 months	1.233	0.665-2.247	0.517
Treatment			
Discontinuation	9.350	5.195-16.830	0.000*
Tapering 50%	3.232	1.832-5.729	0.000*
Duration of remission	0.878	0.797-0.968	0.009*
Sex (male)	0.851	0.448-1.619	0.851
B27 positive	0.716	0.285-1.802	0.479

*Statistically significant ($p<0.05$) features in the multivariate Cox regression analysis. Clinical response in the first 6 months: it is the clinical response when the drug was first used in the patients and before tapering. Disease activity at the start of etanercept: remission (ASDAS<1.3), moderate disease activity (ASDAS ≥1.3 and <2.1), high disease activity (ASDAS ≥2.1 and ≤3.5) and very high disease activity (ASDAS >3.5).

Table V. Clinical features and outcomes of nr-axSpA.

	Discontinuation (n=15)	Tapering 25% (n=30)	Tapering 50% (n=16)
Age, years	30.1 ± 12.7	36.4 ± 13.5	31.3 ± 16.1
male, n %	12 (80.0)	26 (86.7)	15 (93.8)
Disease duration, years	2.2 ± 2.6	3.2 ± 1.7	2.6 ± 1.9
HLA-B27 positive, n %	15 (100)	30 (100)	16 (100)
Relapse 6 months, n%	3 (20.0)	0 (0)	0 (0)
Relapse 12 months, n%	5 (33.3)	1 (3.3)	2 (12.5)
Relapse 18 months, n %	8 (53.3)	3 (10.0)	4 (25)
Relapse 24 months, n %	9 (60.0)	4 (13.3)	6 (37.5)
Remission time before discontinuation or tapering, months	7.1 ± 1.7	7.0 ± 1.4	7.3 ± 2.2

strained the patients from going on with appropriate treatment. Our study demonstrated that tapering of etanercept is much more accommodating compared to discontinuation. The disease recurrence rate is significantly higher in patients stopping etanercept than in those remaining on tapering treatment.

Our findings were consistent with the previous studies indicating discontinuation of anti-TNF therapy leads to spondylitis flare within a few months (6, 21). In the previous studies, different research reported varies of reduction strategies.

It is possible to taper etanercept in axSpA patients while maintaining its efficacy. Some previous studies have reported maintenance of clinical remission on a lower etanercept dose. Such as, reduction of the etanercept dose to 25 mg weekly after a 12-week induction period with standard etanercept 50 mg weekly, or to 25 mg every 10 days, 25 mg every other week, 50 mg every 8 days, etc. (22-24). No significant increase in disease flare-up was found in all of these researches. However, report from Yates *et al*. claimed that tapering dose of 25 mg once a week was less effective at maintaining treatment than standard dose, though more than 50% of the patients remained responders (25). Lee started etanercept at 50 mg/week for 12 weeks and reduced to 25 mg per week for 42 weeks and discontinued (22). Lee *et al*. (23)conducted the reduction strategy by increasing etanercept interval (most frequent regimen 25 mg/ 12 days), Navarro-Compán *et al*. (24) increased etanercept interval (most frequent regimen 25 mg/week) and Cantini *et al*. (18) increased etanercept interval (most frequent regimen 50 mg/2 weeks). Lee claimed that 25 mg per week was as effective as 50mg per week as maintenance therapy. The percentage of patients maintaining LDA or remission after reduction of etanercept dose was 86% (21 months) in the study by Cantini *et al*., which was in accordance with that of the taper 25% group, and higher than that of the taper 50% group in our study. Lee *et al*. and Navarro-Compán *et al*. reported the mean change in disease activity measures after reducing etanercept, which was similar to that of the taper 25% group, and lower than that of the taper 50% group in our study. It seemed that patients in our study had higher relapsed rate than the researches mentioned above at a similar reduction rate of about taper 50%. Race and territory discrepancy, time for exercise and social support may account for it. It also suggested that strategy of taper 50% in our territory may not have the capacity to maintain the same remission/LDA rate as that in other areas.

In order to maintain clinical remission or LDA, the dosing interval of etanercept was gradually increased every 3 months. The patients spaced out the frequency of injection by 25% every 3 months had significantly better outcome than those spaced out 50% every 3 months. Some patients in the spaced out 50% group remained stable or even better. It is feasible to slowly increase the dosing interval and transit to the lowest effective dose or even discontinue finally in some patients. The speed of reduction was related to relapse. Despite the attempts to reduce the etanercept dose, spaced out 50% every 3 months or discontinuation without the process of tapering was not effective enough in some cases and not recommended, several patients insisted on the treatment mostly for economic burdens. Previous use of etanercept has influence on the outcomes of maintenance treatment.

Patients achieving sustained remission for 1 year or more before tapering were at very low risk of relapse. However, the relapse rate of tapering after 6 months of remission is significantly higher. Our data suggested that prolonging the time under remission before tapering would help to improve the outcome. This may be an essential element to the successful tapering strategy.

Unfortunately, it was reported that no evidence of improvement in spine was observed in terms of radiographic disease progression in AS patients treated with etanercept for nearly 2 years (26). As long as the goal of improving symptoms, function, activity index and quality of life is achieved, it is feasible to im-

plement etanercept tapering. Expense of the therapy is one of the main causes of high drop-out rate. Indeed, the balance of less loss of efficacy and saving money helped to improve drug survival in our study. In terms of compliance with therapy and cost-effectiveness, we should consider the quality of life and costs of the disease, including direct costs such as more hospital days and health services or other medications due to relapse and indirect costs such as poor functioning, disability, early retirement and sick leave (27-29).

The choice of appropriate therapy for different countries and territories should be evaluated in the real world. According to the present study, the strategy with the lowest flare rate among the three strategies included in this study, was the strategy of spacing out 25% of the injection frequency of etanercept every 3 months after remission of more than 12 months, if the activity and function parameters were not compromised. It may be a pragmatic approach for more cost-effective use of the drug and made a balance with lowering the flare rate, to some extent.

Still, there is a long way to go for the most appropriate strategy and a lot more research is required.

Conclusion

Tapering of etanercept is much more accommodating compared to discontinuation. It is feasible to slowly increase the dosing interval and transit to the lowest effective dosing interval or even stop finally in some patients, as long as they remained remission or LDA. The speed of reduction was related to relapse. Prolonging the time under remission to >12 months before tapering help to improve the outcome. Among the three strategies included in this study, spacing out 25% of the injection frequency every 3 months after remission of more than 12 months turned out to be a pragmatic approach for more cost-effective use of the drug.

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