Ther Adv Musculoskel Dis
2020, Vol. 12: 1–14
DOI: 10.1177/1759720X20929441

Disease activity guided stepwise tapering or discontinuation of rhTNFR:Fc, an etanercept biosimilar, in patients with ankylosing spondylitis: a prospective, randomized, open-label, multicentric study

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Abstract

Background: The aim of this study was to evaluate disease-activity-guided stepwise tapering or discontinuation of rhTNFR:Fc, an etanercept biosimilar, in patients with ankylosing spondylitis (AS) in a prospective, randomized, open-label, multicentric study.

Methods: Active AS patients with AS disease activity score (ASDAS) ⩾2.1 recruited from 10 hospitals were treated with rhTNFR:Fc 50 mg weekly for 12 weeks, and further randomized into different tapering or discontinuation groups according to ASDAS at week 12. Patients who achieved clinical remission (ASDAS $<$ 1.3) were assigned randomly to stepwise tapering group or discontinuation group. Patients who achieved low disease activity (LDA, 1.3⩽ASDAS $<$ 2.1) were assigned randomly to stepwise tapering, delayed tapering, or discontinuation group. All patients were evaluated every 12 weeks until week 48. The primary endpoint was cumulative flare rates in different groups at week 48.

Results: A total of 311 patients were enrolled with an average ASDAS of 3.6 ± 1.0, and 259 completed 12 weeks of rhTNFR:Fc induction therapy, with 148 patients (57.1%) achieved clinical remission, 100 (38.6%) achieved LDA, and 11 (4.3%) remained as high disease activity (ASDAS⩾2.1). In patients who achieved clinical remission at week 12, stepwise tapering of rhTNFR:Fc demonstrated significantly lower flare rates at each evaluation compared with discontinuation. In patients who achieved LDA, there was no significant difference of flare rates between stepwise tapering, delayed tapering, and discontinuation. With stepwise tapering of rhTNFR:Fc, flare rates were comparable in AS patients, irrespective of initial ASDAS before tapering.

Conclusion: Stepwise tapering of rhTNFR:Fc when patients achieved clinical remission was able to maintain favorable low flare rates in 48 weeks. LDA was an alternative therapeutic target, as well as an viable timing for initiation of rhTNFR:Fc tapering. rhTNFR:Fc 25 mg monthly maintained flare-free status in a considerable number of patients. However, abrupt discontinuation of rhTNFR:Fc even if patients achieved clinical remission should be avoided.

Trial registration: ClinicalTrials.gov: NCT03880968,
URL: https://clinicaltrials.gov/ct2/show/NCT03880968

Keywords: ankylosing spondylitis, disease activity, etanercept biosimilar, tapering

Received: 15 January 2020; revised manuscript accepted: 5 May 2020.

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Introduction

Ankylosing spondylitis (AS), a subset of axial spondyloarthritis (axSpA), is a chronic inflammatory disorder characterized by inflammatory back pain and predominant involvement of sacroiliac joints and spine, leading to bony fusion of vertebrae and, eventually, disability in some patients.[1] Nonsteroidal anti-inflammatory drugs (NSAIDs) are recognized as a first-line therapy for AS,[2] but the overall response rates to NSAIDs are considerably unsatisfactory.[3] With the advent of biologics, the outcomes of AS patients have been greatly improved. Biologics, including tumor necrosis factor α (TNFα) inhibitors (TNFi), have been included in many recommendations for the treatment of AS.[1,2,4,5] Etanercept, a recombinant human TNFα receptor, is capable of binding to TNFα and blocking its biological activities.[6] It is effective in relieving symptoms, improving physical function, and reducing disease activity in patients with AS, and generally no severe adverse effects have been reported.[6,7] However, the high expense of biologics restricts their long-term use, which urges a viable strategy to reduce the dosage of biologics while maintaining an optimal therapeutic efficacy.

Several studies have investigated the tapering and discontinuation strategies for biologics in AS.[8–20] However, when to start tapering or discontinuing biologics, and what is the optimal tapering strategy in AS, remain undetermined. In some studies, dose reduction was initiated on the basis of the time schedule after a certain period of standard etanercept therapy,[8,17] but, in most studies, tapering was considered when remission or low disease activity (LDA) was achieved. Nevertheless, the definitions of remission and LDA have been discrepant across different studies. For instance, some defined remission as Bath ankylosing spondylitis disease activity index (BASDAI) <4,[11,18] whereas some defined remission as BASDAI <2,[13] and in still other studies, LDA was defined as BASDAI <4.[10,14,15,19] Multiple strategies of tapering have also been suggested in different studies, including prolongation of administration intervals, reduction in dosages, or a combination of both. In most studies, the reduced dosage was predetermined and unchanged across the whole observation. Few studies adopted the patient-tailored tapering strategy, and the dosage of etanercept was reduced gradually.[15]

To investigate the stepwise tapering and discontinuation of TNFi based on disease activity in patients with AS, a 48-week, prospective, randomized, multicentric study was conducted. An etanercept biosimilar, rhTNFR:Fc (recombinant TNF receptor: Fc fusion protein, Yisaipu), which is one of the most widely used biosimilars in China, was used in this study.

Methods

Study design

This 48-week prospective, randomized, open-label study was conducted in 10 hospitals in southeast China, including the Second Affiliated Hospital of Zhejiang University School of Medicine, Shanghai Guanghua Integrative Medicine Hospital Affiliated to Shanghai University of Tradition Chinese Medicine, the First Affiliated Hospital of Wenzhou Medical University, the First Hospital of Jiaxing, Shaoxing Second Hospital, Shanghai Jiaotong University Affiliated Sixth People's Hospital, Ningbo Medical Center Lihuili Hospital, Wenzhou Central Hospital, Zhejiang Provincial People's Hospital, and Shaoxing People's Hospital. The trial was designed to evaluate disease activity guided tapering and discontinuation strategies of rhTNFR:Fc. Patients with AS were treated with standard dosage of rhTNFR:Fc for 12 weeks as the induction therapy in the first stage of this study. Afterwards, based on whether patients achieved clinical remission or LDA at the end of 12 weeks, they were further assigned randomly to different tapering or discontinuation groups.

The study was approved by local ethics committee (SAHZU2012-13), and was performed in accordance with Good Clinical Practice guidelines of the International Conference on Harmonization and the principles of the Declaration of Helsinki. This trial was registered [ClinicalTrials.gov identifier: NCT03880968].

Patients

Patients with AS were recruited between 1 March 2012 and 30 September 2013. Eligible patients were aged between 18 years old and 65 years old, and were diagnosed with AS according to 1984 revised New York classification criteria.[21] Inclusion criteria included an active disease of AS disease activity score (ASDAS) using C reactive protein (ASDAS-CRP) $\geqslant 2.1$, a disease duration of 6 months to 30 years, and no exposure to biologics in the 6 months before recruitment. Concomitant medications including NSAIDs, conventional disease

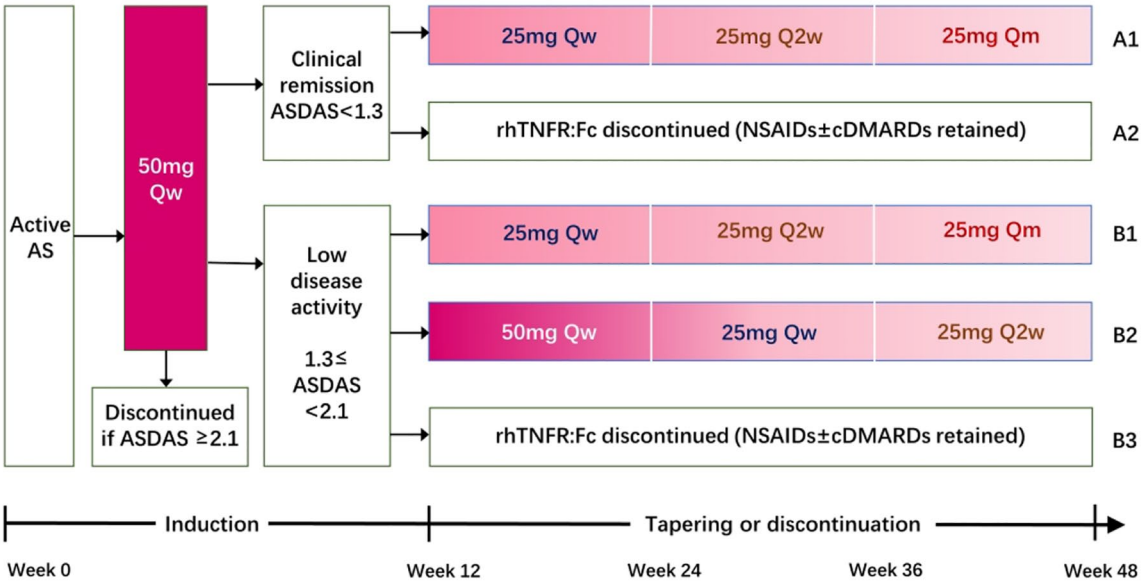

Figure 1. Study design.
Patients with AS enrolled were treated with rhTNFR:Fc 50 mg subcutaneously each week for 12 weeks, and then randomized into subgroups with different tapering or discontinuation strategies according to the ASDAS at the end of week 12.
AS, ankylosing spondylitis; ASDAS, ankylosing spondylitis disease activity score; cDMARDs, conventional disease modifying anti-rheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; Q2w, each two weeks; Qm, each month; Qw, each week.

modifying anti-rheumatic drugs (cDMARDs), or prednisone or a prednisone equivalent (≤10 mg/day) were retained if they had been maintained at a stable dose for at least 4 weeks before recruitment. Patients with late-stage spinal fusion, severe cardiac, hepatic, renal, hematologic or endocrine diseases, multiple sclerosis, current or past malignancies, active or recurrent infections, use of oral antibiotics 2 weeks or intravenous antibiotics 4 weeks before screening, or current or past or potential tuberculosis were excluded. Patients who were pregnant or breastfeeding, or planning to become pregnant were also excluded. Written informed consents were obtained for all patients.

Randomization and masking

Randomization was implemented using a random number table generated by computer, and cards were placed in sealed opaque envelopes (HXW). Randomization lists were kept at each participating center. In patients who achieved clinical remission at the end of induction therapy, they were allocated in a ratio of 3:1 to rhTNFR:Fc stepwise tapering or discontinuation group. In patients who achieved LDA at the end of induction therapy, they were allocated in a ratio of 3:1:1 to rhTNFR:Fc stepwise tapering, delayed tapering, or discontinuation group. Patients and investigators were unblinded once the interventions were assigned. Sample size was calculated based on the risk ratio, and noninferiority tests in the trial arms were performed.

Procedures

In the induction phase of this study (Figure 1), all AS patients were treated with 50 mg rhTNFR:Fc subcutaneously each week for the first 12 weeks. ASDAS (refers to ASDAS-CRP below unless specified otherwise) was then calculated at the end of week 12. Patients who achieved clinical remission with ASDAS < 1.3 were designated as group A, and those achieved LDA with 1.3≤ASDAS < 2.1 as group B (previously 1.3≤ASDAS < 2.1 was recognized as moderate disease activity, but recently LDA was used to indicate status within this range).[22,23]

In the second phase of this study, patients in group A with clinical remission were randomly assigned to stepwise tapering group A1 (treated with rhTNFR:Fc 25 mg weekly for 12 weeks, 25 mg every 2 weeks for 12 weeks, and 25 mg monthly for the last 12 weeks), or discontinuation group A2 (rhTNFR:Fc was discontinued whereas previous concomitant NSAIDs and/or cDMARDs were retained). Patients in group B with LDA were assigned randomly to stepwise tapering group B1 (same tapering strategy as group A1), delayed

tapering group B2 (treated with rhTNFR:Fc 50 mg weekly for another 12 weeks, 25 mg weekly for 12 weeks, and 25 mg every 2 weeks for 12 weeks), and discontinuation group B3 (same discontinuation strategy as group A2) (Figure 1).

Outcomes

The primary endpoint was cumulative flare rates based on ASDAS at week 48 with different tapering or discontinuation strategies. All patients were evaluated at week 0, 12, 24, 36, and 48 for symptoms, physical signs, cotherapies as well as adverse events. ASDAS, BASDAI, Bath AS metrology index (BASMI), and Bath AS functional index (BASFI) were documented, and complete blood count, chemistry panel, CRP, erythrocyte sedimentation rate (ESR), and urinalysis were assayed at each visit. Antinuclear antibody (ANA) and chest radiographs were examined at week 0 and 48. After week 12, flares were defined as ASDAS >2.1,[24] and flared patients restarted rhTNFR:Fc 50 mg weekly with subsequent tapering.

Statistical analysis

Differences in treatment strategies were evaluated by unpaired two-sided *t* test, Wilcox test, ANOVA, or Kruskall–Wallis test ($p<0.05$). Kaplan–Meier analysis was used to estimate the cumulative probability of the relapse rates. Survival curves were generated for different rhTNFR:Fc tapering or discontinuation strategies from week 12 to endpoint. χ^2 test was used to compare cumulative relapse rates, and log-rank test was applied to compare survival curves. Cox proportional hazard model was used to determine baseline predictors that were associated with risks of disease flares. Crude hazard ratios (HRs) were calculated for each candidate characteristic, whereas adjusted HRs were calculated by including redefined statistically significant characteristics ($p<0.10$) in one model simultaneously, or adjusted for statistically significant variables at baseline when comparing relapse rates in a disease activity guided manner. All analyses were done using R Statistical Software, version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients characteristics

A total of 311 patients with active AS were recruited, with 223 men and 88 women and an average age of 31.0 ± 11.3 years old. ASDAS was 3.6 ± 1.0 (range 2.1–6.4) at inclusion. All patients were managed with rhTNFR:Fc 50mg subcutaneously each week, and 259 patients completed induction therapy with rhTNFR:Fc for 12 weeks. At the end of week 12, 148 (57.1%) patients achieved clinical remission (ASDAS <1.3) with the absolute change of ASDAS from week 0 ($|\Delta$ASDAS$|$) ranging from 0.9 to 4.5, 100 (38.6%) achieved LDA ($1.3 \leqslant$ASDAS <2.1) with $|\Delta$ASDAS$|$ from 0.1 to 3.9, and 11 (4.3%) remained high disease activity (ASDAS >2.1). Subsequently, 142 patients with clinical remission and 93 patients with LDA were randomized to different tapering or discontinuation groups. Patients with high disease activity despite rhTNFR:Fc for 12 weeks withdrew from the study and switched to other medications (Figure 2). The characteristics of patients in subgroups were comparable at the end of week 12 before they were further randomized with different therapeutic strategies (Table 1).

At the end of week 48, a total of 183 AS patients completed the study, with 33 patients flared and 150 remaining flare-free. From week 12 to week 48, 52 patients withdrew from the study, mostly because of loss to follow up. rhTNFR:Fc was generally safe without severe adverse events. Only five mild adverse events were reported, including two cases with leukopenia, two cases with abnormal liver function, and one case with injection site reaction; all recovered shortly after discontinuing rhTNFR:Fc.

Flare rates with different tapering or discontinuation strategies

The cumulative flare rates were calculated every 12 weeks until the end of week 48. In patients who achieved clinical remission at week 12 with subsequent stepwise tapering of rhTNFR:Fc (A1), the flare rate increased over time when rhTNFR:Fc was gradually tapered every 12 weeks, from 1.0% at week 24, to 4.3% at week 36, and 9.0% at week 48. When compared with patients who discontinued rhTNFR:Fc (A2), patients in the A1 groups with stepwise tapering had significantly lower flare rates at each time point of evaluation (supplemental Table S1). The average time to flare from the initiation of tapering or discontinuation was 28.5 ± 9.0 weeks in A1, and 18.86 ± 9.44 weeks in A2 ($p=0.06$) (Figure 3). In patients who achieved LDA at week 12 (B1, B2, B3), the cumulative flare rates all increased over

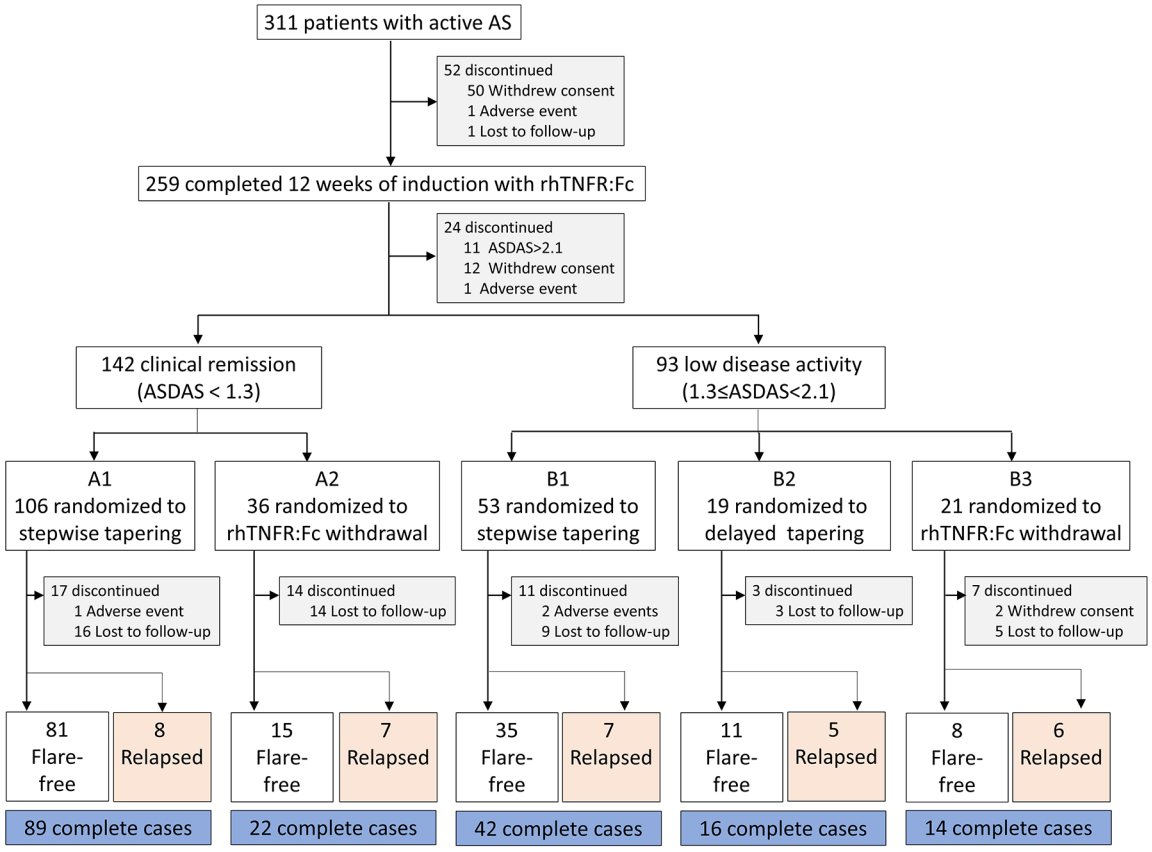

Figure 2. Study profile.
Patients were randomized to different tapering or discontinuation groups according to the disease activity at week 12.
AS, ankylosing spondylitis; ASDAS, ankylosing spondylitis disease activity score; cDMARDs, conventional disease modifying anti-rheumatic drugs; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 1. Demographics, disease characteristics and concomitant medications at the end of week 12.

Characteristics	A1 (*n* = 106)	A2 (*n* = 36)	*p* value	B1 (*n* = 53)	B2 (*n* = 19)	B3 (*n* = 21)	*p* value
Male, *n* (%)	68 (64.2)	26 (72.2)	0.42	42 (79.3)	10 (52.6)	13 (61.9)	0.07
Age (year)	30.1 ± 10.4	29.7 ± 10.7	0.84	33.5 ± 12.2	33.1 ± 8.9	32.5 ± 10.2	0.94
Disease duration (month)*	39 (23, 77)	24 (12, 73)	0.50	60 (28, 87)	72 (54, 131)	38 (16, 61)	0.18
ESR (mm/h)*	5 (3, 11)	5 (2, 8)	0.46	11 (3, 18)	7.5 (4, 27.8)	11 (7, 17)	0.74
CRP (mg/l)	1.9 ± 1.7	1.5 ± 1.1	0.36	6.8 ± 6.0	5.5 ± 4.4	6.3 ± 4.8	0.69
NSAIDs ± cDMARDs, *n* (%)	38 (35.9)	19 (52.8)	0.08	15 (28.3)	5 (26.3)	11 (52.4)	0.12

*Median (first quartile, third quartile).
Normal distributed data was demonstrated as mean ± SD.
cDMARDs, conventional disease modifying anti-rheumatic drugs; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation.

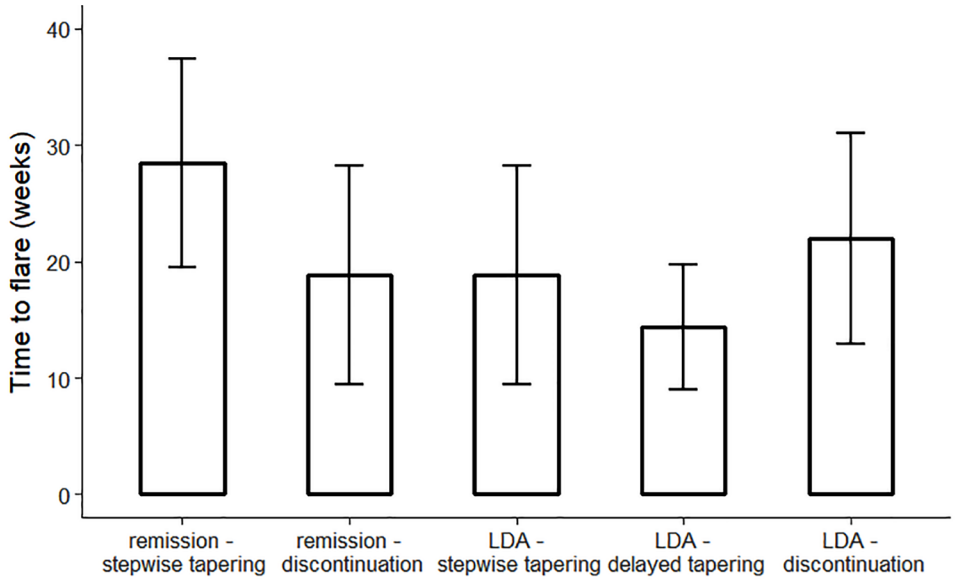

Figure 3. Average time to flare with different tapering or discontinuation strategies.
The average flare time in patients with different tapering or discontinuation strategies, including patients with remission who initiated stepwise tapering, or discontinuation of rhTNFR:Fc, and patients with LDA who initiated stepwise tapering, delayed tapering, or discontinuation. The error bars represent standard deviation.
LDA, low disease activity.

time, but there was no significant difference among three groups at each time point (supplemental Table S1). No significant difference of average time to flare was identified among B subgroups (Figure 3). Likewise, when survival curves were generated using Kaplan–Meier approach and evaluated by log-rank test, significant difference between A1 and A2 was noticed, whereas no significance among B subgroups was indicated (Figure 4).

For patients who shared the same tapering strategy, those who achieved clinical remission before reducing the dosage (A1) demonstrated lower flare rate as well as prolonged average time to flare than those who achieved LDA when tapering was initiated (B1) (supplemental Table S1, Figure 3). However, when patients with same strategies were compared using Cox regression analysis after adjusting baseline ASDAS and ESR, there was no significant difference of flare rates between A1 and B1, or between A2 and B3 (Table 2).

Risk factors of disease flares during rhTNFR:Fc tapering or discontinuation

To identify the risk factors of flares during tapering or discontinuation, Cox regression analysis was applied to evaluate the parameters before reduction or discontinuation of rhTNFR:Fc. In patients who achieved clinical remission (A), discontinuation of rhTNFR:Fc, high levels of CRP, and severe stage of sacroiliitis were risk factors for future relapse. However, no risk factors were identified in group B (Table 3).

Sensitivity analysis

Considering that patients withdrew in the rhTNFR:Fc discontinuation groups due mainly to poorer compliance, sensitivity analysis was performed to evaluate the robustness of our results. By assuming that all the patients who withdrew from the study experienced a disease flare, sensitivity analysis demonstrated roughly similar results (supplemental Tables S2 and S3).

Discussion

Several studies have investigated the strategies of dosage tapering or discontinuation for biologics in AS patients. However, no extensively accepted agreement has been established, and the optimal timing to start tapering as well as favorable tapering strategies are yet to be investigated. At least 13 prospective or retrospective studies have focused on the tapering or discontinuation of etanercept in AS, with follow-up duration varying

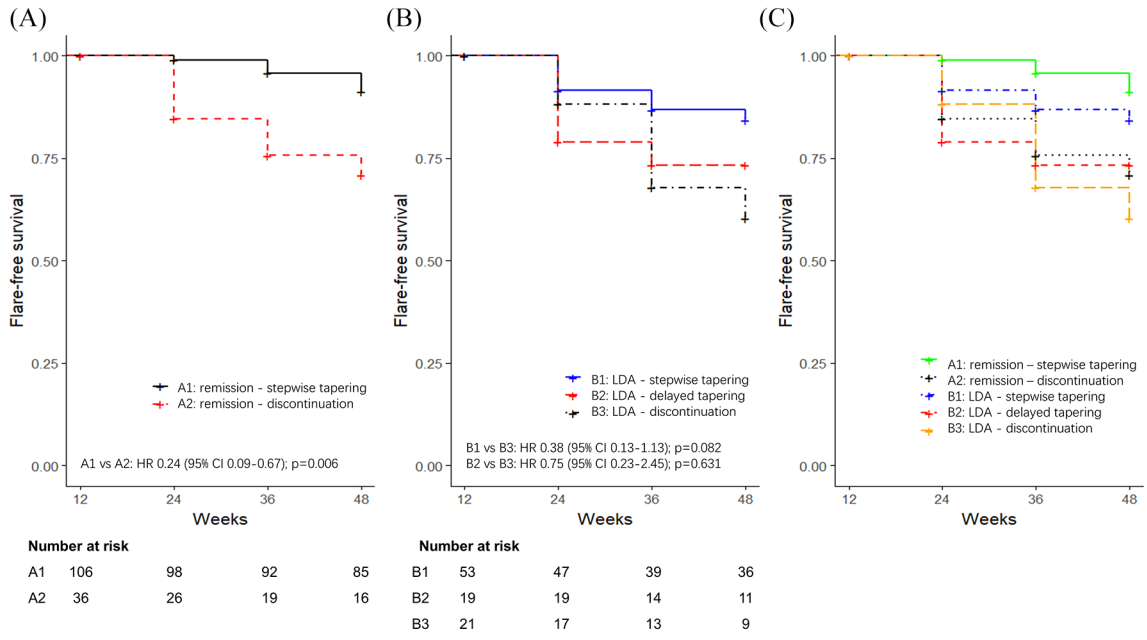

Figure 4. Flare-free survival rates.
Flare-free survival rates in patients with different tapering or discontinuation strategies: (A) patients with clinical remission (ASDAS < 1.3) at week 12. (B) Patients with low disease activity (1.3⩽ASDAS<2.1) at week 12. (C) Patients with both inactive or low disease activity at week 12.
LDA, low disease activity.

Table 2. Disease activity guided comparison of flare rates between groups with the same tapering strategy.

Characteristics	*n*	Crude HR (95% CI)	*p* value	Adjusted HR (95% CI)[a]	*p* value
Subgroup A1	106	Ref	Ref	–	–
Subgroup B1	53	1.99 (0.72–5.49)	0.18	0.93 (0.23–3.73)	0.91
Subgroup A2	36	Ref	Ref	–	–
Subgroup B3	21	1.35 (0.45–4.02)	0.59	0.49 (0.09–2.68)	0.41

[a]Adjusted by ASDAS and ESR level.
ASDAS, ankylosing spondylitis disease activity score; CI, confidence interval; ESR, erythrocyte sedimentation rate; HR hazard ratio.

from 8 weeks to 36 months and the maintenance rate of remission or LDA as 47–86.3% (Table 4).[8–20] According to a systemic review and a meta-analysis on etanercept tapering in AS patients, etanercept reduction was effectively comparable with nondecreasing standard dosages in most studies.[25,26] In our study, the flare-free maintenance rates with stepwise tapering of rhTNFR:Fc at week 48 were 91.0% and 83.3% in patients with clinical remission and LDA, respectively. When to start tapering etanercept in AS patients has been inconsistent among recommendations or studies. According to the 2016 updates of management recommendations for axSpA, tapering of biologics could be considered if the patient was in sustained remission, which was defined as inactive disease based on ASDAS for 6 months or longer.[2] But in the 2018 update of French society for rheumatology (SFR) recommendations, other than patients with disease remission for at least 6 months, those with low level of activity were also qualified for dose reduction.[27] To our knowledge, our study is the first to investigate the tapering timing in the same research by dichotomizing patients into subgroups according to disease activity. Tapering at clinical remission or LDA were both evaluated. When the same tapering strategy was applied to patients with different disease status, patients with initial clinical remission demonstrated lower cumulative flare rates and prolonged time to

Table 3. Risk factors of flare before rhTNFR:Fc tapering or discontinuation.

Characteristics	*n*	Crude HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
Group A					
Subgroup A1	106	0.24 (0.09–0.67)	0.01	0.19 (0.06, 0.61)	0.01
Subgroup A2	36	Ref	Ref	–	–
Gender					
Male	94	Ref	Ref	–	–
Female	48	0.72 (0.23–2.27)	0.59	–	–
Age	140	0.99 (0.94–1.04)	0.74	–	–
Disease duration	138	1.00 (0.99–1.01)	0.83	–	–
ESR	142	0.93 (0.83–1.04)	0.18	–	–
CRP	142	1.29 (1.00–1.65)	0.05	1.46 (1.11, 1.93)	0.01
White blood cell	141	0.99 (0.90–1.09)	0.84	–	–
Hemoglobin	141	1.00 (0.97–1.04)	0.91	–	–
Platelets	140	1.00 (0.99–1.01)	0.67	–	–
Peripheral arthritis	141	0.51 (0.12–2.28)	0.38	–	–
Sacroiliitis stage	121	2.04 (0.94–4.45)	0.07	2.64 (1.09, 6.38)	0.03
ASDAS-C	140	1.75 (0.33–9.44)	0.51	–	–
Group B					
Subgroup B1	53	0.38 (0.13–1.13)	0.08	0.43 (0.14, 1.35)	0.15
Subgroup B2	19	0.75 (0.23–2.45)	0.63	–	–
Subgroup B3	21	Ref	Ref	–	–
Gender					
Male	65	Ref	Ref	–	–
Female	28	0.76 (0.25–2.30)	0.62	–	–
Age	92	1.01 (0.97–1.05)	0.61	–	–
Disease duration	93	1.00 (1.00–1.01)	0.35	–	–
ESR	92	1.02 (0.99–1.06)	0.21	–	–
CRP	93	1.04 (0.98–1.11)	0.22	–	–
White blood cell	91	1.09 (0.81–1.48)	0.57	–	–
Hemoglobin	92	0.99 (0.96–1.02)	0.63	–	–
Platelets	92	1.01 (1.00–1.01)	0.11	1.01 (1.00, 1.01)	0.11
Peripheral arthritis	93	0.74 (0.29–1.88)	0.53	–	–
Sacroiliitis stage	77	0.87 (0.40–1.88)	0.72	–	–
ASDAS-C	93	2.41 (0.50–11.6)	0.27	–	–

Crude HRs were calculated in Cox regression models that included only one independent variable at a time. Adjusted HRs were calculated in a multivariable Cox regression model that included all redefined statistically significant variables ($p < 0.10$) at once.
ASDAS-C, ankylosing spondylitis disease activity score using CRP; CI, confidence interval; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HR hazard ratio.

Table 4. Studies on ETN tapering or discontinuation in AS patients.

Authors	Study design	Country	Number of patients	Follow up after tapering	Timing of tapering	Tapering strategies	Evaluating tools	Results
Lee *et al.*[8]	Prospective	Korea	27	6 months	3 months	50 mg weekly for 3 months, then 25 mg weekly for 6 months	BASDAI, CRP, ESR	After discontinuation, time to flare 9.2 ± 6.1 weeks
Lee *et al.*[9]	Retrospective	Korea	109	18 months	BASDAI reduction of at least 50% or absolute decrease of more than 2 units (0–10 scale)	Mean dosing interval was 4.7 ± 2.1 days at 3 months and was increased to 12.1 ± 7.0 days at 21 months	BASDAI, CRP	At endpoint, etanercept survival rate was 98%. The mean BASDAI and mean CRP declined during follow up
Navarro-Compán *et al.*[10]	Prospective	Spain	51	26.1 ± 21 months	Achievement of LDA, defined as BASDAI < 4, and CRP normal values (<5 mg/l).	25 mg weekly in 25%, 25 mg every 10 days in 6.3%, 25 mg every other week in 12.5%, 50 mg every 8 days in 18.7% and 50 mg every 10 days in 37.5% patients	BASDAI, CRP	Remained in clinical remission with BASDAI values < 2 and normal CRP values
Cantini *et al.*[11]	Prospective	Italy	78	22 ± 1 months	Remission defined as BASDAI < 4, no extra-axial manifestations, and normal acute-phase reactants.	50 mg every other week	BASDAI	86.3% in halving group and 90.4% in no dose reduction group were in remission
De Stefano *et al.*[12]	Prospective	Italy	38	36 weeks	Clinical partial remission: value of <2 on a 1–10 point scale in each of four ASAS domain, score BASDAI <2, absence of inflammatory manifestations, normal CRP	25 mg weekly at week 12 and 16, then 25 mg every other week at week 24 and 28 if still in remission	ASAS 20, ASAS 40, ASAS 5/6	47% still in remission
Plasencia *et al.*[14]	Retrospective	Spain	74	12 months	Sustained LDA of at least 6 months, defined by BASDAI < 4, and also fulfilled one of these conditions: normal CRP or ΔBASDAI > 50%	ETN was delayed 3 days for a maximum of 3 weeks	BASDAI	81.8% maintained LDA; flare rate with ETN was 27%

(Continued)

Table 4. (Continued)

Authors	Study design	Country	Number of patients	Follow up after tapering	Timing of tapering	Tapering strategies	Evaluating tools	Results
Arends *et al.*[15]	Prospective	Netherlands	39	24 months	Stable LDA (BASDAI < 4) for at least 6 months	Patient-tailored (step-by-step approach)	BASDAI, ASDAS, CRP	LDA (ASDAS < 2.1) in 90% before start and 77% after 24 months. Inactive disease (ASDAS < 1.3) in 55% and 53% of patients, respectively
Almirall *et al.*[13]	Prospective	Spain	8	12 months	Remission defined by BASDAI ⩽ 2, no peripheral joint disease and normal CRP levels	50 mg every 10 days or 25 mg every week	BASDAI, CRP	50% of patients with etanercept remained in remission or LDA
Yates *et al.*[16]	Prospective	United Kingdom	59	6 months	Responders defined by 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	25 mg weekly	BASDAI	20 (83%) of the 50 mg arm maintained clinical response compared with 12 (52%) of the 25 mg arm
Li *et al.*[17]	Prospective	China	43	2 months	4 weeks	50 mg weekly for 4 weeks, then 25 mg weekly for 8 weeks	BASDAI, CRP, ESR	Mean BASDAI scores reduced from 4.82 ± 0.69 to 1.42 ± 0.23
Park *et al.*[18]	Prospective	Korea	134	6 months–4.41 years	Clinical remission, with BASDAI < 4 and CRP < 0.5 mg/dl	No consistent regimen for dose adjustment	BASDAI, CRP	Overall 2-, 3- and 4-year drug survivals in the low-dose group were 98%, 91.0% and 83.4%
Zavada *et al.*[19]	Prospective	Czech Republic	53	12 months	LDA(BASDAI < 4) after at least 6 months of treatment	Prolong the administration interval, reduce the dose or both approaches	BASDAI, CRP, BASFI, HAQ	The HR (95% CI) of reduced *versus* standard dosing group for relapse was 1.46 (0.66–3.19)
Zhao *et al.*[20]	Prospective	China	35	36 months	ASAS 20 response	Withdrawal	ASAS20, BASDAI	The cumulative probabilities of relapse at 1, 2, and 3 years were 45.7, 57.1, and 60.0%; Median time to flare 15 months

AS, ankylosing spondylitis; ASAS, assessment in ankylosing spondylitis; BASDAI, Bath AS disease activity index; BASFI, Bath AS functional index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; ETN, etanercept; LDA, low disease activity; HAQ, health assessment questionnaire; VAS, visual analogue scale.

relapse when compared with those with initial LDA. After adjustment with ASDAS and ESR, there was no significant difference between these two groups of patients, suggesting that LDA can also be considered as an appropriate timing for the initiation of rhTNFR:Fc dosage reduction. Besides, it further confirms that low/minimal disease activity may be an alternative treatment target.[28]

Other than the timing of, or the disease activity status before, tapering, the specific procedures of reducing etanercept dosage was critically essential in clinical practice. The maximal interval of etanercept injection in the above mentioned 13 studies was 3 weeks at a dosage of 25 mg,[14] while, in others, 25 mg weekly or every 2 weeks was applied. The minimal dosage in our study, 25 mg each month, has not been documented in any previous research. When rhTNFR:Fc was reduced from 25 mg every 2 weeks to 25 mg each month for 12 weeks, the cumulative flare rate increased from 4.3% to 9.0% in patients who were in clinical remission before tapering, and from 14.0% to 16.7% in those with LDA before tapering. Whether rhTNFR:Fc 25 mg each month can sustainably maintain LDA or clinical remission of longer duration should be investigated in further studies.

One previous study evaluated the discontinuation of etanercept in AS patients who achieved ASAS20, and the cumulative probabilities of relapse at 1, 2, and 3 years were 45.7, 57.1, and 60.0%, respectively.[20] In our study, when rhTNFR:Fc was discontinued, the flare rate was 31.8% after 36 weeks in patients with clinical remission, and 42.9% in patients with LDA. Irrespective of the disease status patients had achieved before rhTNFR:Fc tapering or discontinuation, if the rhTNFR:Fc was discontinued, the relapse rates increased over time, even if the NSAIDs and/or cDMARDs were retained. Discontinuation of rhTNFR:Fc was identified as one of the risk factors of disease flare in patients with clinical remission, indicating that abrupt discontinuation of rhTNFR:Fc should be avoided. Longer duration of remission before tapering or gradual dosage reduction before discontinuation may be investigated.

Multiple parameters have been developed to evaluate the disease activity of AS, including the BASDAI, BASFI, BASMI, ASAS, and ASDAS. Most of the above mentioned studies on etanercept tapering used BASDAI or ASAS to define disease activity status, and only one study also included ASDAS as an assessment.[15] According to the 2017 update of recommendations on treating spondyloarthritis to target, ASDAS is a preferred measure in axSpA as it is more associated with various biomarkers of inflammation than BASDAI and correlates better with magnetic resonance imaging (MRI) changes.[28] ASDAS has also been considered as highly discriminatory in the detection of therapeutic differences and improvement from baseline.[29] Our study used ASDAS, and it was correlated highly with BASDAI (data not shown). We did not measure the biomarkers of inflammation or MRI changes, so whether ASDAS outweighs BASDAI on evaluations during rhTNFR:Fc tapering needs further investigation.

The cutoff values of ASDAS were updated in 2018 by ASAS. ASDAS < 1.3 remained as inactive, and $1.3 \leqslant$ ASDAS < 2.1, previously indicating moderate disease activity, was considered as LDA.[23] Flare was defined as ASDAS $\geqslant 2.1$ in our study,[24] but we also evaluated a compound definition of flares, with ASDAS $\geqslant 2.1$ for patients with LDA, and ASDAS $\geqslant 1.3$ as well as ΔASDAS $\geqslant 0.6$ for patients with clinical remission. It was more complicated, seemingly more reasonable, and tailored to individual subgroups when compared with the single criteria of ASDAS $\geqslant 2.1$ in all patients, yet this combined definition for flares did not change the results (data not shown). Another definition of clinical important worsening in axSpA was an increase in ASDAS of at least 0.9 points,[30] which was also applied to evaluate the flares in our patients, and the conclusions remained unchanged (data not shown).

It is noteworthy that, at the end of induction therapy for 12 weeks, only 4.3% patients remained with high disease activity, whereas the majority achieved either remission or LDA. A possible explanation is that 50 patients withdrew consent before completion of induction therapy at week 12 (Figure 2), with some complaining of inconvenience, lack of efficacy, and other reasons. Presumably, some of them should remain in high disease activity status at week 12 even if they continued with the induction therapy. As they did not return at week 12 for evaluation, the actual disease activity they had was unknown. The proportions we observed were based on the number of patients who completed 12-week induction therapy.

There are some limitations of our study. This trial was completed by the end of 2014, and it took a long time to publish the results, due mainly to the time-consuming data extraction from all case report forms, the unexpected resignation of the initial statistician for personal reasons, and multiple revisions before submission. Of the 259 patients who finished the initial 12-week rhTNFR:Fc induction, only 183 (70.7%) completed the study at week 48. The compliance of patients should be more carefully monitored to improve the follow-up rate. Besides, the flare rates in the delayed tapering group (B2) were higher than those in stepwise tapering group (B1), even though there was no significant difference between these two groups on the flare rates at each evaluation. We currently do not have a reasonable explanation for this phenomenon, and more patients in group B2 should probably be included for further observation. The tapering of rhTNFR:Fc was observed for only 36 weeks, and whether longer duration of low-dose rhTNFR:Fc was effective warrants future investigation. Lastly, comparisons between groups would also be clearer and more direct if we had included an arm with standard dose of rhTNFR:Fc throughout the trial. However, the current arms in this study represent several commonly used methods of tapering and discontinuation in patients who have to reduce or discontinue rhTNFR:Fc for various reasons, and our results provide evidence of optimal strategies in these clinical scenarios.

To conclude, our study suggested that disease-activity-guided stepwise tapering strategy of rhTNFR:Fc in AS patients is applicable. rhTNFR:Fc stepwise tapering when patients achieved clinical remission was able to maintain favorable flare-free rates across week 48. LDA is an alternative therapeutic target, as well as an appropriate timing for initiation of rhTNFR:Fc dosage reduction. rhTNFR:Fc 25mg each month was capable of maintaining flare-free status in a considerable number of patients and warrants future investigation. Abrupt discontinuation of rhTNFR:Fc was associated with high flare rates and should be avoided regardless of the disease activity status that patients have reached.

Acknowledgments

We thank all participants and employees of participating centers for their time and effort.

Contributors

TZ, DYH, XWC, HZW, YZ, QX, WLL, GBX, YSL, ZMY, and HXW contributed to study design and data collection. TZ and JNZ performed data analyses. All authors contributed to data interpretation and writing of the manuscript. All authors approved the final manuscript for submission.

Data sharing

Individual deidentified participants' data that underlie the results reported, the study protocol, statistical analysis plan, and analytical code are available with publication to researchers who provide a methodologically sound proposal to achieve aims in the approved proposal or for individual participant data meta-analysis. Proposals should be directed to wuhx8855@zju.edu.cn; to gain access, data requestors will need to sign a data access agreement.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by 3SBIO Inc., which provided some rhTNFR:Fc used in this study. The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

References

1. Taurog JD, Chhabra A and Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. *N Engl J Med* 2016; 374: 2563–2574.

2. van der Heijde D, Ramiro S, Landewe R, *et al.* 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017; 76: 978–991.

3. Cinar M, Dinc A, Simsek I, *et al*. Evaluation of the short-term efficacy of NSAIDs on patients with active ankylosing spondylitis in daily practice: a 3-month, longitudinal, observational study. *Rheumatol Int* 2010; 30: 331–340.
4. Ward MM, Deodhar A, Akl EA, *et al*. American college of rheumatology/spondylitis association of America/spondyloarthritis research and treatment network 2015 recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2016; 68: 282–298.
5. Ward MM, Deodhar A, Gensler LS, *et al*. 2019 update of the American college of rheumatology/spondylitis association of America/spondyloarthritis research and treatment network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2019; 71: 1599–1613.
6. Liu YF, Dong H, Tu SH, *et al*. Etanercept in the treatment of ankylosing spondylitis: a systematic review and meta-analysis. *Exp Ther Med* 2014; 8: 1585–1592.
7. Li ZH, Zhang Y, Wang J, *et al*. Etanercept in the treatment of ankylosing spondylitis: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials, and the comparison of the Caucasian and Chinese population. *Eur J Orthop Surg Traumatol* 2013; 23: 497–506.
8. Lee SH, Lee YA, Hong SJ, *et al*. Etanercept 25 mg/week is effective enough to maintain remission for ankylosing spondylitis among Korean patients. *Clin Rheumatol* 2008; 27: 179–181.
9. 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: 1149–1154.
10. Navarro-Compán V, Moreira V, Ariza-Ariza R, *et al*. Low doses of etanercept can be effective in ankylosing spondylitis patients who achieve remission of the disease. *Clin Rheumatol* 2011; 30: 993–996.
11. Cantini F, Niccoli L, Cassara E, *et al*. 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.
12. De Stefano R, Frati E, De Quattro D, *et al*. Low doses of etanercept can be effective to maintain remission in ankylosing spondylitis patients. *Clin Rheumatol* 2014; 33: 707–711.
13. Almirall M, Salman-Monte TC, Lisbona MP, *et al*. Dose reduction of biological treatment in patients with axial spondyloarthritis in clinical remission: are there any differences between patients who relapsed and to those who remained in low disease activity? *Rheumatol Int* 2015; 35: 1565–1568.
14. Plasencia C, Kneepkens EL, Wolbink G, *et al*. Comparing tapering strategy to standard dosing regimen of tumor necrosis factor inhibitors in patients with spondyloarthritis in low disease activity. *J Rheumatol* 2015; 42: 1638–1646.
15. Arends S, van der Veer E, Kamps FB, *et al*. Patient-tailored dose reduction of TNF-α blocking agents in ankylosing spondylitis patients with stable low disease activity in daily clinical practice. *Clin Exp Rheumatol* 2015; 33: 174–180.
16. Yates M, Hamilton LE, Elender F, *et al*. Is Etanercept 25 mg once weekly as effective as 50 mg at maintaining response in patients with ankylosing spondylitis? A randomized control trial. *J Rheumatol* 2015; 42: 1177–1185.
17. Li J, Wang X, Han Z, *et al*. Dose reduction of recombinant human tumor necrosis factor inhibitors (etanercept) can be effective in ankylosing spondylitis patients with synovitis of the hip in a Chinese population. *Int J Immunopathol Pharmacol* 2016; 29: 510–505.
18. Park JW, Yoon YI, Lee JH, *et al*. Low dose etanercept treatment for maintenance of clinical remission in ankylosing spondylitis. *Clin Exp Rheumatol* 2016; 34: 592–599.
19. 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.
20. Zhao M, Zhang P, Fang L, *et al*. Possible predictors for relapse from etanercept discontinuation in ankylosing spondylitis patients in remission: a three years' following-up study. *Clin Rheumatol* 2018; 37: 87–92.
21. van der Linden S, Valkenburg HA and Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361–368.
22. Machado P, Landewe R, Lie E, *et al*. Ankylosing spondylitis disease activity score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis* 2011; 70: 47–53.

23. Machado PM, Landewe R, Heijde DV; Assessment of SpondyloArthritis International Society (ASAS). Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. *Ann Rheum Dis* 2018; 77: 1539–1540.

24. Gossec L, Portier A, Landewe R, *et al*. Preliminary definitions of 'flare' in axial spondyloarthritis, based on pain, BASDAI and ASDAS-CRP: an ASAS initiative. *Ann Rheum Dis* 2016; 75: 991–996.

25. Edwards CJ, Fautrel B, Schulze-Koops H, *et al*. Dosing down with biologic therapies: a systematic review and clinicians' perspective. *Rheumatology (Oxford)* 2017; 56: 1847–1856.

26. Lee H, Jung Y, Song S, *et al*. Dosage and duration of etanercept therapy for ankylosing spondylitis: a meta-analysis. *Int J Technol Assess Health Care* 2017; 33: 69–75.

27. Wendling D, Lukas C, Prati C, *et al*. 2018 update of French society for rheumatology (SFR) recommendations about the everyday management of patients with spondyloarthritis. *Joint Bone Spine* 2018; 85: 275–284.

28. Smolen JS, Schols M, Braun J, *et al*. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis* 2018; 77: 3–17.

29. van der Heijde D, Braun J, Dougados M, *et al*. Sensitivity and discriminatory ability of the ankylosing spondylitis disease activity score in patients treated with etanercept or sulphasalazine in the ASCEND trial. *Rheumatology (Oxford)* 2012; 51: 1894–1905.

30. Molto A, Gossec L, Meghnathi B, *et al*. An assessment in spondyloarthritis international society (ASAS)-endorsed definition of clinically important worsening in axial spondyloarthritis based on ASDAS. *Ann Rheum Dis* 2018; 77: 124–127.