The Journal of Rheumatology 2023;xx:xxxxx
doi:10.3899/jrheum.220353
First Release January 15 2023

The Journal of Rheumatology

Etanercept Withdrawal and Retreatment in Nonradiographic Axial Spondyloarthritis: Results of RE-EMBARK, an Open-Label Phase IV Trial

Filip Van den Bosch[1], James Cheng-Chung Wei[2], Peter Nash[3], Francisco J. Blanco[4], Daniela Graham[5], Chuanbo Zang[6], Edmund Arthur[7], Cecilia Borlenghi[8], Vassilis Tsekouras[9], Bonnie Vlahos[10], and Atul Deodhar[11]

ABSTRACT. ***Objective.*** RE-EMBARK investigated etanercept (ETN) withdrawal and retreatment in patients with nonradiographic axial spondyloarthritis (nr-axSpA) achieving inactive disease.

Methods. Patients received ETN and a background nonsteroidal antiinflammatory drug for 24 weeks in period 1 (P1); those achieving inactive disease (Ankylosing Spondylitis Disease Activity Score [ASDAS] with C-reactive protein [CRP] < 1.3) discontinued ETN for 40 weeks or less (period 2 [P2]). Patients who flared (ASDAS with erythrocyte sedimentation rate [ESR] ≥ 2.1) were retreated for 12 weeks in period 3 (P3). The primary endpoint was the proportion of patients with inactive disease who flared within 40 weeks of ETN withdrawal. Baseline characteristics were analyzed post hoc as predictors of maintenance and regaining of inactive disease, respectively, using univariate logistic and stepwise multivariable logistic regression models.

Results. The proportion of patients experiencing flare following ETN withdrawal (P2) increased from 22.3% (25/112) after 4 weeks to 67% (77/115) after 40 weeks; 74.8% (86/115) experienced flare at any time during P2. Median time to flare was 16.1 weeks. Most patients (54/87, 62.1%) who were retreated with ETN in P3 reachieved inactive disease. Absence of both sacroiliitis detected on magnetic resonance imaging (MRI) and high-sensitivity CRP (hs-CRP) > 3 mg/L at baseline predicted inactive disease maintenance in P2 following ETN withdrawal in multivariable analysis; male sex and age younger than 40 years predicted regaining of inactive disease in P3 after flare/retreatment. There were no unexpected safety signals.

Conclusion. Approximately 25% of patients maintained inactive disease for 40 weeks after discontinuing ETN. Absence of both MRI sacroiliitis and high hs-CRP at baseline predicted response maintenance after ETN withdrawal. (ClinicalTrials.gov: NCT02509026)

Key Indexing Terms: ankylosing spondylitis, biological therapy, etanercept, nonradiographic axial spondyloarthritis, retreatment

This study was sponsored by Pfizer.

[1]F. Van den Bosch, MD, PhD, Department of Internal Medicine and Pediatrics, Ghent University, and VIB Center for Inflammation Research, Ghent, Belgium; [2]J.C.C. Wei, MD, PhD, Department of Allergy, Immunology & Rheumatology, Chung Shan Medical University Hospital, Institute of Medicine, College of Medicine, Chung Shan Medical University, and Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan; [3]P. Nash, MD, Department of Medicine, Griffith University, Brisbane, Australia; [4]F.J. Blanco, MD, PhD, Universidad de A Coruña, Grupo de Investigación de Reumatología (GIR), INIBIC – Complejo Hospitalario Universitario de A Coruña, SERGAS, Departamento de Fisioterapia y Medicina, A Coruña, Spain; [5]D. Graham, MD, Global Product Development, Pfizer, Groton, Connecticut, USA; [6]C. Zang, PhD, Global Biometrics and Data Management, Pfizer, Collegeville, Pennsylvania, USA; [7]E. Arthur, PharmD, Clinical Development and Operations, Pfizer, Peapack, New Jersey, USA; [8]C. Borlenghi, MD, Inflammation & Immunology, Pfizer Global Medical Affairs, Buenos Aires, Argentina; [9]V. Tsekouras, MD, PhD, Inflammation & Immunology, Pfizer Global Medical Affairs, Strovolos, Cyprus; [10]B. Vlahos, BSN, MBA, Global Product Development, Pfizer, Collegeville, Pennsylvania, USA; [11]A. Deodhar, MD, Division of Arthritis & Rheumatic Diseases, Oregon Health & Science University, Portland, Oregon, USA.

FVdB reports grant/research support from AbbVie, Merck, and UCB; and consulting fees from AbbVie, BMS, Celgene, Eli Lilly, Galapagos, Gilead, Janssen, MoonLake, Novartis, Pfizer, and UCB. JCCW reports grant/research support from AbbVie, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, and UCB; and consulting fees from TSH Biopharm, AbbVie, BMS, Celgene, Chugai, Eisai, Janssen, Novartis, Pfizer, Sanofi-Aventis, and UCB Pharma. PN reports grant/research support from AbbVie, BMS, UCB, Lilly, Roche, Sanofi, Pfizer, Janssen, Gilead, and Novartis; reports consulting fees from AbbVie, BMS, UCB, Lilly, Roche, Sanofi, Pfizer, Janssen, Gilead, and Novartis; and is on the speakers bureau for AbbVie, BMS, UCB, Lilly, Roche, Sanofi, Pfizer, Janssen, Gilead, and Novartis. FJB reports grant/research support from Sanofi-Aventis, Lilly, BMS, Amgen, Pfizer, AbbVie, TRB Chemedica International, GSK, Archigen Biotech Limited, Novartis, Nichi-Iko Pharmaceutical, Genentech, Janssen Research & Development, UCB Biopharma, Centrexion Therapeutics, Celgene, Roche, Regeneron Pharmaceuticals, Biohope, Corbus Pharmaceutical, Tedec Meiji Pharma, Kiniksa Pharmaceuticals, and Gilead Sciences; and consulting fees from Lilly, BMS, Grunenthal, and Pfizer. DG, CZ, EA, CB, VT, and BV are employees of Pfizer and hold Pfizer stock. AD reports grant/research support from AbbVie, Eli Lilly, GSK, Novartis, Pfizer, and UCB; and consulting fees from Amgen, AbbVie, Aurinia, BI, Celgene, Eli Lilly, GSK, Janssen, MoonLake, Novartis, Pfizer, and UCB.

Address correspondence to Dr. F. Van den Bosch, Universitair Ziekenhuis Gent – Dienst Reumatologie (University Hospital Ghent – Department of Rheumatology), Corneel Heymanslaan 10, B-9000 Ghent, Belgium. Email: filip.vandenbosch@ugent.be.

Accepted for publication November 9, 2022.

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease predominantly affecting the axial skeleton; the stage without definitive radiographic sacroiliitis is termed *non-radiographic disease* (ie, nr-axSpA).[1] AxSpA treatment guidelines recommend biologic disease-modifying antirheumatic drugs (bDMARDs) when the disease is not controlled by nonsteroidal antiinflammatory drugs (NSAIDs), initially with a tumor necrosis factor inhibitor (TNFi).[2-5] The efficacy of the TNFi etanercept (ETN) in nr-axSpA was demonstrated by the EMBARK trial,[6-8] where patients receiving ETN for 12 weeks showed rapid, significant improvements in disease activity[6] that were maintained long term.[7,8]

The 2016 Assessment of SpondyloArthritis international Society (ASAS)–European Alliance of Associations for Rheumatology axSpA recommendations suggest tapering bDMARDs in "sustained remission," with Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease proposed as a definition of clinical remission, but they stop short of endorsing stopping treatment completely.[2] Similarly, the 2018 Asia Pacific League of Associations for Rheumatology axSpA treatment guidance does not recommend stopping treatment completely.[3] The 2019 American College of Rheumatology recommendations for nr-axSpA advise against tapering of biologics as a standard approach.[4]

Patients with axSpA typically have disease onset early in life[9] and are likely to start TNFi treatment early; therefore, treatment withdrawal upon achieving inactive disease is especially relevant. Data on outcomes following treatment cessation, as well as understanding which patients might best respond, would be highly informative to patients and physicians. For ETN, clinical trial data remain sparse regarding maintenance of "remission" in nr-axSpA after treatment discontinuation.

RE-EMBARK was a postapproval study requested by the European Medicines Agency to assess the frequency of flare after ETN withdrawal among patients with inactive disease and the efficacy and safety of retreatment after flare. Post hoc analyses explored baseline predictors of maintenance of inactive disease following ETN withdrawal and predictors of regaining inactive disease following flare and ETN retreatment.

METHODS

Study design and participant selection. RE-EMBARK (ClinicalTrials.gov: NCT02509026) was a multicenter, open-label, 3-period study that ran from September 2015 through September 2019. Patients with nr-axSpA enrolled at 62 sites across 14 countries (Figure 1). In period 1 (P1), all patients were treated with subcutaneous ETN 50 mg once weekly for 24 weeks, plus a stable background NSAID at the optimal tolerated antiinflammatory dosage per the investigator. Patients who achieved ASDAS with C-reactive protein (ASDAS-CRP) < 1.3 at week 24 (therapeutic target) entered period 2 (P2), a 40-week withdrawal period where patients discontinued ETN but maintained background NSAID. Patients who flared before week 64 entered a 12-week retreatment period (period 3 [P3]) with ETN 50 mg once weekly.

Eligible patients were aged 18 to 49 years with active (ie, ASDAS-CRP ≥ 2.1) nr-axSpA as diagnosed by their rheumatologist, which fulfilled the ASAS axSpA classification criteria, but without definitive radiographic sacroiliitis according to the modified New York criteria. All radiographs and magnetic resonance imaging (MRI) scans were centrally read. Full inclusion and exclusion criteria, which were similar to those of EMBARK,[6] are provided in the Supplementary Materials (available with the online version of this article).

Ethics and consent. The protocol and informed consent documentation were reviewed and approved by the Institutional Review Board and/or Independent Ethics Committee at each of the participating investigational sites (Supplementary Table S1, available with the online version of this article). There was no specific primary ethics committee for the study. Not all ethics committees used reference numbers; therefore, the study protocol number (B1801381) was used as reference. The study was conducted in compliance with the ethical principles originating in, or derived from, the Declaration of Helsinki and in compliance with all International Council for Harmonisation Good Clinical Practice Guidelines, and all local regulatory requirements were followed. All patients provided written informed consent to participate before study activities were initiated. No patients or members of the public were involved in the design of, recruitment to, or conduct of this study.

Study outcomes. The primary objective was to estimate the proportion of patients who flared within 40 weeks following ETN withdrawal among patients who achieved an ASDAS-CRP < 1.3 (ie, inactive disease). Flare was defined as an ASDAS with erythrocyte sedimentation rate (ASDAS-ESR) score ≥ 2.1. ASDAS-ESR was used for flare instead of ASDAS-CRP because results were available during patient visits, allowing immediate treatment decisions in the clinic.

A key prespecified secondary objective was estimation of time to flare after ETN withdrawal compared with patients in the EMBARK study who met the entry requirements specified for the withdrawal period of RE-EMBARK (ie, achieved ASDAS-CRP < 1.3) but continued ETN therapy. Other secondary objectives evaluated the efficacy of ETN over 24 weeks of initial treatment and the efficacy of 12 weeks of ETN retreatment in patients who experienced flare after ETN withdrawal. These were based on the following endpoints: ASDAS-CRP < 1.3; ASAS20 and ASAS40; ASAS partial remission; ASDAS-CRP and ASDAS-ESR scores; ASDAS-CRP major improvement and clinically important improvement; nocturnal and total back pain; Bath Ankylosing Spondylitis Functional Index and its components; Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and its components; BASDAI50; CRP; ESR; Maastricht Ankylosing Spondylitis Enthesitis Score; swollen and tender joint counts (44 joints); EQ-5D, 36-item Short Form Health Survey, and Work Productivity and Activity Impairment; and Spondyloarthritis Research Consortium of Canada (SPARCC) sacroiliac joint (SIJ) and spine MRI scores. Safety was a secondary objective, based on treatment-emergent adverse events (TEAEs) and serious TEAEs.

Statistical analysis of primary and secondary endpoints. Sample size was determined based on primary and secondary endpoints, with the following assumptions: (1) for P1, an ASDAS-CRP inactive disease rate of 48% was assumed based on data from EMBARK, where the ASDAS-CRP inactive disease rate at week 24 was 47% for patients treated with ETN[6]; (2) for P2, a flare rate of 70% was assumed based on the ESTHER study, where 69% of patients treated with ETN flared after 1 year of withdrawal[10]; and (3) for P3, an ASDAS-CRP inactive disease rate of 60% was assumed based on data from ETN in pediatric patients with psoriasis,[11] where 58% of patients with disease relapse achieved a Psoriasis Area and Severity Index-75 (PASI75) scores after 12 weeks of ETN retreatment. Enrollment of 200 patients was expected to result in 96 entering treatment withdrawal, and 70% were expected to flare following withdrawal, giving a half-width of the 95% CI on flare rate estimate of approximately 10%.

Binary endpoints were summarized as numbers, percentages, and 95% CIs. For continuous endpoints, raw and change-from-baseline data were summarized using descriptive statistics. P1 baseline values were defined as the last available value of the screening and baseline visits. The P2 baseline was defined as the last value before treatment withdrawal. The P3 baseline was defined as the last P2 value before retreatment. *P* values for

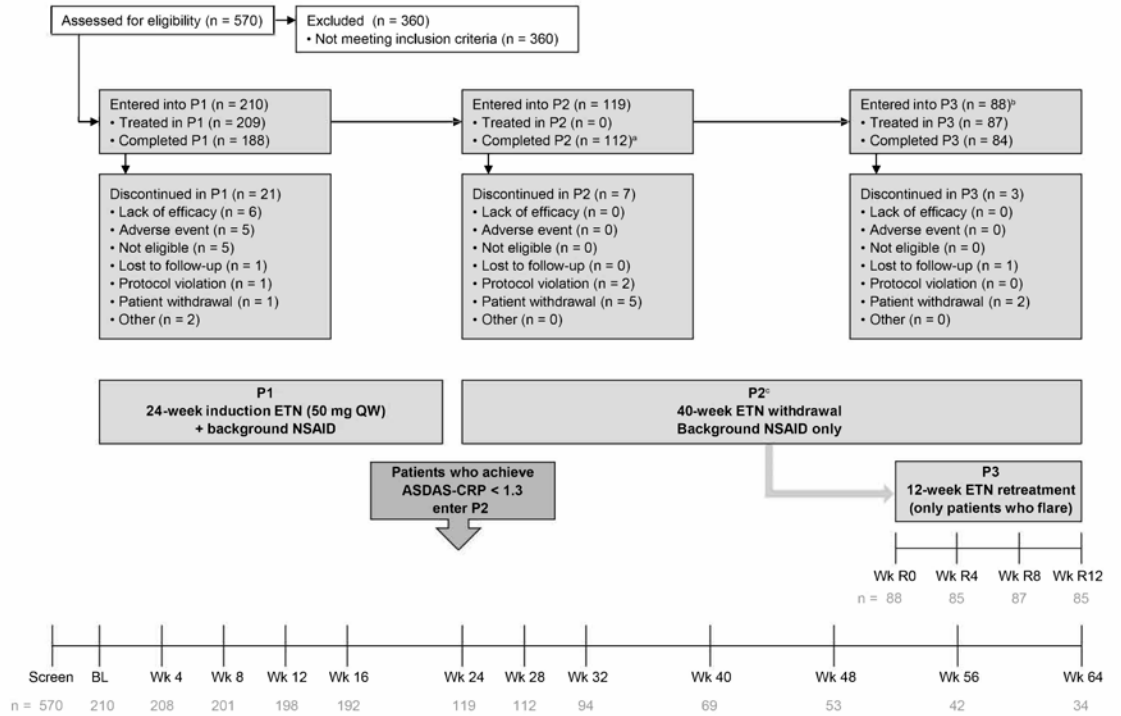

Figure 1. [a] Patients were classified as P2 "completers" if they completed P2 without disease flare or if they flared at any time and moved to P3. [b] A total of 86 patients who experienced disease flare entered P3, plus 2 who did not flare (1 patient flared according to site ASDAS-ESR calculations but not final programming calculations, and 1 had a protocol violation). Although 88 patients entered Period 3, 1 patient withdrew from the study before treatment due to reason of "no longer willing to participate." [c] The primary endpoint was the occurrence of flare (ASDAS-ESR ≥ 2.1) within 40 weeks following withdrawal of ETN (in P2). ASDAS: Ankylosing Spondylitis Disease Activity Score; BL: baseline; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ETN: etanercept; NSAID: nonsteroidal antiinflammatory drug; P: period; QW: once weekly; R: retreatment; Wk: week.

change-from-baseline data were calculated using the paired *t* test. Analyses were performed for observed and last observation carried forward (LOCF) data, but no baseline values were carried forward. The Kaplan-Meier approach was used to estimate the median time to event and corresponding 95% CIs, and to produce Kaplan-Meier plots. The Kaplan-Meier approach and life chart with the log-rank test for significance compared RE-EMBARK and EMBARK data. Cox proportional hazards models estimated the hazard ratio of RE-EMBARK vs EMBARK, with study and baseline characteristics as covariates.

Post hoc analysis of baseline predictors. Demographic and disease characteristics at screening or P1 baseline were analyzed post hoc as categorical predictors of the maintenance of inactive disease and regaining inactive status in patients who entered P2 and P3, respectively, using univariate logistic regression and stepwise multivariable logistic regression models. For the stepwise regression, *P* values of 0.5 and 0.05 were used for variables to be included and to remain in the model, respectively. Significant predictors were identified and kept in the final model, while nonsignificant factors were subtracted. Analyses were based on observed cases.

The following baseline factors that were considered potential response predictors for TNFi[12-21] were included in the univariate and multivariable analyses for P2 and P3: age (< 40 yrs vs ≥ 40 yrs), BMI (calculated as weight in kilograms divided by height in meters squared; < 25 vs ≥ 25), symptom duration (< 2 yrs vs ≥ 2 yrs), enthesitis (no enthesitis vs enthesitis), HLA-B27 status (negative vs positive), high-sensitivity CRP (hs-CRP; ≤ 3 mg/L vs > 3 mg/L), sacroiliitis on MRI at screening (negative vs positive), MRI SIJ SPARCC score (≤ 2 vs > 2), positive MRI plus hs-CRP > 3 mg/L (yes vs no), race (non-White vs White), sex, and weight (< 70 kg vs ≥ 70 kg).

RESULTS

Patients. A total of 209 patients were treated with open-label ETN in P1; 119 (56.9%) achieved inactive disease and entered the ETN withdrawal period (P2). Whereas 88 patients entered the ETN retreatment period (P3), 1 patient was not treated and not included in the safety or full analysis set for P3 (Figure 1).

Patient demographics and disease characteristics at P1 baseline are summarized in Table 1. Mean ASDAS-CRP and ASDAS-ESR scores at baseline were indicative of high to very high disease activity. Patient demographics were similar across the 3 periods (Supplementary Table S2, available with the online version of this article); however, the percentage of males was slightly higher in P2 (63.9%) and P3 (63.2%) than in P1 (53.6%).

Patient demographics at RE-EMBARK P2 baseline were generally comparable to those of the EMBARK study after 24 weeks of ETN treatment, although more EMBARK patients were male (73.3% vs 64.3%) and Asian (27.6% vs 5.2%) and fewer were White (67.6% vs 91.3%; Supplementary Table S3, available with the online version of this article). Disease characteristics following 24 weeks of ETN treatment were broadly similar for RE-EMBARK and EMBARK; where differences were noted, disease burden was usually higher in EMBARK than in RE-EMBARK.

Table 1. Patient demographics and disease characteristics at P1 baseline.

	P1 Baseline Values, N = 209
Age, yrs	33.1 (8.2)
Sex, male, n (%)	112 (53.6)
Race, n (%)	
White	186 (89)
Black	1 (0.5)
Asian	14 (6.7)
Other	8 (3.8)
BMI[a]	26.8 (5.8)
HLA-B27 positive, n (%)	162 (77.5)
Positive MRI sacroiliitis by ASAS criteria, n (%)	142 (67.9)
HLA-B27 positive and positive MRI sacroiliitis by ASAS criteria, n (%)	96 (45.9)
Elevated CRP, n (%)	138 (66)
Duration of disease symptoms, yrs	1.9 (1.5)
Family history of SpA, n (%)	37 (17.7)
ASDAS-CRP	3.5 (0.9)
ASDAS-ESR	3.6 (0.9)
BASDAI total score (1-10)	6.4 (1.8)
BASFI total score (1-10)	4.7 (2.2)
CRP, mg/L	12.6 (20.8)
ESR, mm/h	26.7 (23.6)
MASES total score	2.9 (3.0)
SJC-44	2.3 (3.0)
TJC-44	6.0 (5.4)
Nocturnal back pain VAS	5.9 (2.5)
Total back pain VAS	6.0 (2.4)
Inflammation, cm	6.4 (2.1)
EQ-5D VAS	48.6 (21.2)
SF-36 MCS score	44.2 (10.7)
SF-36 PCS score	33.3 (7.1)
Patient assessment of disease activity, cm	6.3 (2.1)
Physician global assessment, cm	6.1 (1.9)
WPAI	50.8 (28.1)
SPARCC MRI SIJ score	8.5 (12.8)
SPARCC MRI 6 DVU spinal score	2.6 (6.7)
Inflammatory back pain, n (%)	199 (95.2)
Arthritis, n (%)	98 (46.9)
Enthesitis, n (%)	89 (42.6)
Psoriasis, n (%)	22 (10.5)
Anterior uveitis, n (%)	15 (7.2)

Data are in mean (SD) unless otherwise indicated. [a] BMI is calculated as weight in kilograms divided by height in meters squared. ASAS: Assessment of SpondyloArthritis international Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; DVU: discovertebral unit; ESR: erythrocyte sedimentation rate; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; MCS: mental component summary; MRI: magnetic resonance imaging; P1: period 1; PCS: physical component summary; SF-36: 36-item Short Form Health Survey; SIJ: sacroiliac joint; SJC-44: swollen joint count-44 joints; SpA: spondyloarthritis; SPARCC: Spondyloarthritis Research Consortium of Canada; TJC-44: tender joint count-44 joints; VAS: visual analog scale; WPAI: Work Productivity and Activity Impairment.

Efficacy of ETN during initial treatment (P1). At week 24 (ie, end of P1), 58.7% (122/208) of patients achieved inactive disease (Figure 2), with 24.4% (51/209) achieving sustained inactive disease (ASDAS-CRP < 1.3 at weeks 12 or 16 and week 24); 119 of these 122 patients continued to P2 (ie, ETN withdrawal). A significant decrease in ASDAS-CRP scores was observed at all P1 postbaseline visits (ie, weeks 4-24; Supplementary Table S4, available with the online version of this article).

Flare within 40 weeks of ETN withdrawal (P2). The proportion of patients experiencing flare increased during P2 from 22.3% (25/112; data for 3 patients not available) at week 28 to 67% (77/115) at week 64 (LOCF, P2 baseline values not carried forward; Figure 3A). An additional 9 patients experienced flare between P2 visits, so overall, 86 out of 115 patients (74.8%) flared within the 40 weeks following ETN withdrawal. These patients immediately entered P3 and restarted ETN. Fewer patients with (49/72, 68.1%) vs without (37/43, 86.0%) sustained responses during P1 experienced flare after ETN withdrawal.

Whereas 50% of RE-EMBARK patients experienced flare within 16.1 (95% CI 12.6-24.0) weeks (approximately 113 days) of ETN withdrawal, less than 25% of patients from EMBARK who met the RE-EMBARK criteria for ETN withdrawal but continued ETN treatment experienced flare over 40 weeks (Figure 3B). Time to flare was significantly shorter in patients who discontinued ETN treatment in RE-EMBARK vs patients who continued ETN treatment in EMBARK ($P < 0.0001$; Supplementary Table S5, available with the online version of this article). Patients in EMBARK who continued ETN treatment had an 85% reduction in risk of experiencing flare vs patients in RE-EMBARK who discontinued ETN (hazard ratio 0.15, 95% CI 0.09-0.24; Cox proportional model).

Time to inactive disease after ETN retreatment (P3). In total, 87 patients were treated in P3. By P3 end, 62.1% (54/87) of patients who were retreated with ETN for 12 weeks reachieved inactive disease, and 50% who reachieved inactive disease in P3 did so within 5.1 (95% CI 4.3-8.1) weeks (Kaplan-Meier analysis).

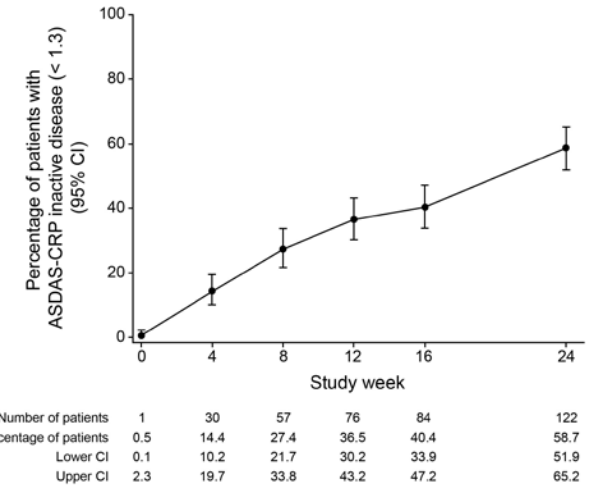

Figure 2. Proportion of patients with inactive disease in P1. ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C-reactive protein; P1: period 1.

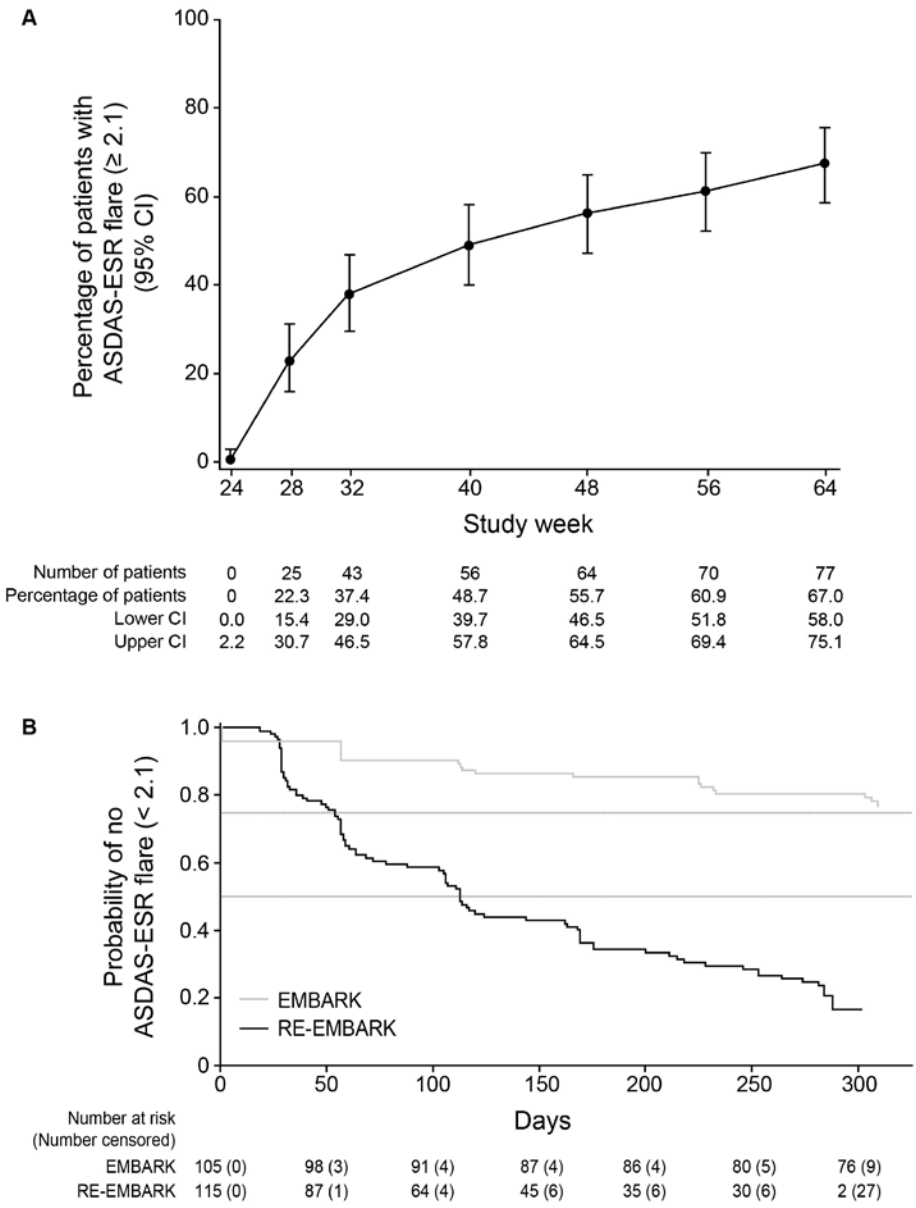

Figure 3. Proportion of patients[a] who flared within 40 weeks of ETN withdrawal (primary endpoint) (A) and Kaplan–Meier plot of the distribution of time-to-ASDAS flare (ASDAS-ESR ≥ 2.1) during the 40-week withdrawal of ETN in RE-EMBARK and during 40 weeks without withdrawal of ETN in EMBARK (B). [a] Patient data were available for 115 patients at each week except for week 28 (data for 112 patients available); baseline values (from week 24) were not carried forward. ASDAS: Ankylosing Spondylitis Disease Activity Score; ESR: erythrocyte sedimentation rate; ETN: etanercept.

Additional secondary efficacy endpoints. There was a trend of improvement with ETN treatment in P1, worsening disease following ETN withdrawal in P2, and improvement in P3 with ETN retreatment illustrated by the changing proportion of patients with inactive disease throughout RE-EMBARK (Supplementary Figure S1, available with the online version of this article). This trend was also observed across clinical, functional, and quality-of-life secondary outcome measures, with the exception of the mean 44-joint tender joint count (Table 2).

Baseline predictors of inactive disease maintenance following ETN withdrawal (P2). In univariate analyses, having hs-CRP ≤ 3 mg/L (odds ratio [OR] 3.30, 95% CI 1.14-9.52; $P = 0.03$) and the absence of both positive MRI and hs-CRP > 3 mg/L (OR 6.62, 95% CI 1.43-30.53; $P = 0.02$) at P1 baseline were associated with maintenance of inactive disease following ETN withdrawal in P2 (Supplementary Table S6, available with the online version of this article), whereas other demographic factors, including sex, age, race, BMI, MRI sacroiliitis status, MRI SIJ SPARCC score, presence of enthesitis, and disease duration, were not associated.

Table 2. Secondary outcome measures.

	End of P1 (Week 24)			End of P2 (Week 64)			End of P3 (Week R12)		
	n/N (%) or n	95% CI	Mean (SD)	n/N (%) or n	95% CI	Mean (SD)	n/N (%) or n	95% CI	Mean (SD)
ASDAS									
Major improvement[a]	102/208 (49.0)	42.3-55.8	–	21/113 (18.6)	12.3-26.5	–	47/87 (54.0)	43.6-64.2	–
Clinically important improvement[b]	161/208 (77.4)	71.4-82.7	–	57/113 (50.4)	41.3-59.6	–	69/87 (79.3)	69.9-86.8	–
ASAS									
ASAS20	173/208 (83.2)	77.7-87.8	–	79/102 (77.5)	68.7-84.7	–	75/87 (86.2)	77.8-92.2	–
ASAS40	149/208 (71.6)	65.2-77.4	–	64/102 (62.7)	53.1-71.7	–	67/87 (77.0)	67.4-84.9	–
Partial remission[c]	121/208 (58.2)	51.4-64.7	–	42/102 (41.2)	32.0-50.9	–	46/87 (52.9)	42.4-63.1	–
BASDAI 50	156/208 (75.0)	68.8-80.5	–	48/115 (41.7)	33.0-50.9	–	72/87 (82.8)	73.8-89.6	–
EQ-5D									
VAS > 82[d]	99/207 (47.8)	41.1-54.6	–	31/108 (28.7)	20.8-37.7	–	43/86 (50.0)	39.6-60.4	–
Improvement from baseline of ≥ 0.05	159/207 (76.8)	70.7-82.2	–	66/108 (61.1)	51.7-69.9	–	71/86 (82.6)	73.5-89.4	–
Change from period baseline									
ASDAS-CRP	208	–	−2.02 (1.15)	113	–	1.46 (1.07)	85	–	−1.61 (1.04)
ASDAS-ESR	208	–	−2.05 (1.17)	115	–	1.52 (1.12)	87	–	−1.83 (0.90)
BASDAI total score	208	–	−4.41 (2.49)	115	–	3.33 (2.82)	87	–	−3.96 (2.42)
BASFI total score	208	–	−3.10 (2.54)	114	–	2.27 (2.51)	86	–	−2.83 (2.24)
CRP, mg/L	208	–	−9.28 (18.90)	114	–	5.42 (11.28)	85	–	−3.38 (8.36)
ESR, mm/h	208	–	−15.44 (23.17)	115	–	6.78 (12.92)	87	–	−7.24 (10.76)
MASES	206	–	−1.55 (2.64)	107	–	0.75 (1.55)	79	–	−1.08 (1.61)
SJC-44	96	–	−1.92 (3.52)	47	–	0.04 (2.37)	18	–	−0.72 (2.02)
TJC-44	96	–	−3.15 (5.26)	47	–	−0.09 (3.74)	18	–	−1.72 (2.52)
Nocturnal back pain VAS	208	–	−4.14 (2.88)	114	–	3.08 (3.06)	86	–	−4.25 (2.74)
Total back pain VAS	208	–	−4.05 (2.79)	114	–	3.10 (3.02)	86	–	−4.15 (2.72)
EQ-5D index score	207	–	0.37 (0.37)	108	–	−0.21 (0.27)	80	–	0.27 (0.31)
EQ-5D VAS	207	–	27.73 (26.74)	108	–	−26.40 (30.51)	80	–	32.08 (26.25)
SF-36 MCS score	190	–	8.39 (10.69)	105	–	−4.84 (8.31)	73	–	4.24 (7.61)
SF-36 PCS score	190	–	12.14 (9.37)	105	–	−10.32 (9.64)	73	–	11.36 (8.61)
WPAI	137	–	−29.93 (29.27)	87	–	25.06 (29.49)	64	–	−29.69 (26.24)
SPARCC SIJ MRI score	143	–	−6.08 (11.71)	29	–	1.45 (4.43)	46	–	−1.96 (8.84)
SPARCC spine MRI score	144	–	−1.52 (5.62)	30	–	0.77 (2.01)	44	–	−0.70 (2.21)

All data are LOCF. [a] Change in ASDAS-CRP score of ≥ 2.0 units. [b] Change in ASDAS-CRP score of ≥ 1.1 units. [c] A value of 20 on the 0 to 100–mm scale in each of the 4 ASAS20 domains. [d] Population norm. ASAS: Assessment of SpondyloArthritis international Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASDAI 50: a 50% improvement in the initial BASDAI; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LOCF: last observation carried forward; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; MCS: mental component summary; MRI: magnetic resonance imaging; P1: period 1; P2: period 2; P3: period 3; PCS: physical component summary; R12: retreatment at week 12; SF-36: 36-item Short Form Health Survey; SIJ: sacroiliac joint; SJC-44: swollen joint count-44 joints; SPARCC: Spondyloarthritis Research Consortium of Canada; TJC-44: tender joint count-44 joints; VAS: visual analog scale; WPAI: Work Productivity and Activity Impairment.

In multivariable analysis, the absence of a combination of positive MRI and hs-CRP greater than 3 mg/L at P1 study baseline was a significant predictor of maintaining inactive disease following ETN withdrawal (OR 6.58, 95% CI 1.42-30.43; $P = 0.02$; Figure 4).

Baseline predictors of regaining inactive disease following flare/retreatment (P3). Univariate analyses showed that male sex (OR 6.86, 95% CI 2.39-19.65; $P < 0.001$), age < 40 years (OR 7.64, 95% CI 2.53-23.03; $P < 0.001$), and the absence of enthesitis (OR 3.10, 95% CI 1.12-8.06; $P = 0.03$) at P1 baseline were associated with regaining inactive disease status following retreatment (Supplementary Table S6, available with the online version of this article).

In multivariable analysis, male sex (OR 5.46, 95% CI 1.68-17.72; $P = 0.005$) and age < 40 years (OR 8.10, 95% CI 2.10-31.20; $P = 0.002$) significantly predicted the regaining of inactive disease following retreatment (Figure 4).

Safety. In total, 70.3% of patients in P1 vs 31.1% in P2 and 33.3% in P3 had a TEAE; 2.9%, 0.8%, and 0%, respectively, reported a serious TEAE in each period (Supplementary Table S7, available with the online version of this article). In total, 6 (2.9%) patients withdrew because of TEAEs, all in P1. Viral upper respiratory tract infection was the most common TEAE during all 3 periods (15.8%, 4.2%, and 9.2%, respectively). There was 1 (0.5%) serious infection in P1. Few patients reported prespecified TEAEs of clinical importance, including flares of inflammatory bowel disease (n = 1), psoriasis (n = 1), and uveitis (n = 2; Supplementary Table S7, available with the online version of this article).

DISCUSSION

RE-EMBARK was designed to prospectively evaluate the effect of ETN withdrawal on disease flare in patients with nr-axSpA

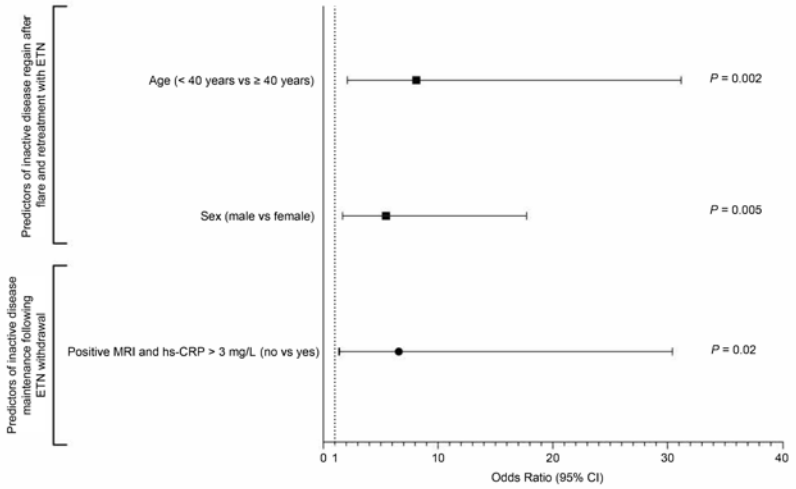

Figure 4. Odds ratios for significant baseline[a] predictors of response maintenance in P2[b] (bottom panel) and inactive disease after flare and retreatment in P3 (top panel) based on multivariate analysis. [a] Characteristics at baseline of P1. [b] A total of 119 patients achieved inactive disease in P1, entered P2 and had ETN withdrawn; however, 4 patients had no efficacy evaluation during P2 and were therefore excluded from the predictor analysis. ETN: etanercept; hs-CRP: high-sensitivity C-reactive protein; MRI: magnetic resonance imaging; P: period.

who were in an inactive disease state. Post hoc analyses explored baseline predictors of the maintenance of inactive nr-axSpA disease following ETN withdrawal and predictors of regaining inactive disease status after ETN retreatment.

Two prior studies investigated ETN discontinuation in patients with axSpA: a post hoc analysis of a small randomized controlled trial of ETN vs sulfasalazine (ESTHER),[10] and a single-center retrospective cohort study.[22] In ESTHER, 9 out of 13 patients who achieved remission after 48 weeks of ETN treatment flared within 60 weeks of discontinuation. By week 108, 5 out of 9 patients who flared achieved ASAS partial remission with ETN retreatment. In RE-EMBARK, a retreatment response rate with ETN of 62% was observed over a relatively shorter treatment duration (12 vs 60 weeks). In the retrospective cohort study, more patients who discontinued ETN relapsed over 6 months compared with patients who tapered doses.[22] However, only 19% of patients relapsed within 6 months of ETN withdrawal. This lower relapse rate relative to that in ESTHER could be partly because of differences in treatment before withdrawal. In the Lian et al[22] study, patients achieved clinical remission for 6 months before discontinuing treatment, whereas in RE-EMBARK, patients with ASDAS-CRP < 1.3 at week 24 discontinued ETN. Although patients were treated with ETN for a similar amount of time in both studies, only 24% of patients in RE-EMBARK achieved sustained inactive disease, whereas others experienced inactive disease for a short period before ETN withdrawal; fewer patients with sustained responses experienced flare compared with ESTHER.

An early, aggressive, treat-to-target approach is recommended in axSpA to improve outcomes.[23] Another benefit of this strategy may determine whether some patients can maintain remission after expensive biologic treatment is discontinued. Results from RE-EMBARK suggest that treatment goals can be achieved even after ETN discontinuation in some (ie, 25%) patients. Studies of other TNFi medications—infliximab (IFX),[24] adalimumab (ADA),[25] certolizumab pegol (CZP),[26] and ixekizumab[27]—demonstrated sustained responses in a portion of patients with axSpA following treatment withdrawal. Moreover, many patients in remission and who flared following withdrawal regained inactive disease status after retreatment. The observational REMINEA study of IFX for ankylosing spondylitis (AS) found that 58% of patients in persistent clinical remission (BASDAI ≤ 2 for 6-12 months) suffered relapse (BASDAI ≥ 4) during withdrawal, and 52% reachieved remission when IFX was restarted.[24] The ABILITY-3 study of ADA for nr-axSpA reported that 47% of patients in sustained remission (ASDAS < 1.3 at weeks 16, 20, 24, and 28) did not flare during 40 weeks after discontinuation, and 57% regained ASDAS inactive disease status after 12 weeks of ADA retreatment.[25] The C-OPTIMISE study of CZP for early axSpA reported that 20% of patients who achieved sustained remission (ASDAS < 1.3) over 48 weeks of open-label treatment before switching to placebo did not flare for a further 48 weeks. After 12 weeks of open-label retreatment, 63% of patients who flared regained clinical remission.[26] In the COAST-Y study, 55% of patients with axSpA who were in remission following ixekizumab treatment flared within 64 weeks of ixekizumab withdrawal.[27] Many patients regained ASDAS low disease activity status (93%) or inactive disease status (44%) after 16 weeks of retreatment. These studies, together with RE-EMBARK, suggest that approximately 50% to 80% of patients experience disease flare after TNFi withdrawal, but around 52% to 63% regain response once TNFi is restarted, and this happens quickly (within 12 weeks). The current treatment paradigm for axSpA is "continuous treatment."[2,4] Studies such as RE-EMBARK challenge this paradigm, suggesting that

the need for maintenance treatment may vary by patient group after induction of remission.

Half of the RE-EMBARK patients who achieved inactive disease maintained ASDAS-ESR < 2.1 (ie, low disease activity) over at least 16 weeks following ETN withdrawal. As temporary treatment discontinuations may be necessary (eg, planned surgery), these data can inform shared decision making regarding treatment interruptions and provide some reassurance that ETN interruptions of 16 weeks or less may be associated with sustained responses in a substantial portion of patients.

Our analyses of baseline predictors of inactive disease maintenance after ETN withdrawal suggest that patients with both hs-CRP and MRI positivity at baseline, indicative of more severe disease, are significantly less likely to maintain inactive disease status following ETN withdrawal compared with patients with either negative MRI or normal hs-CRP. However, double positivity did not significantly affect the odds of achieving inactive disease upon ETN retreatment. Patients who are positive for only 1 of these factors at baseline may be more likely to maintain inactive disease status following ETN withdrawal.

Male sex and age younger than 40 years were significant predictors of regaining inactive disease after a flare and subsequent 12-week retreatment with ETN. Younger age is also a significant predictor of better response to TNFi in patients with AS.[28,29] Sex-specific differences in disease activity in patients with axSpA have been reported: females generally present with higher disease activity, more pain, and worse quality of life.[30] Composite ASDAS scores were similar across sexes; however, this is likely driven by sex differences in the individual components, with higher CRP levels in men and higher scores on other components in women.[30,31] Nevertheless, sex was not a factor associated with maintenance of inactive disease following ETN withdrawal.

Study limitations include the open-label design and absence of a control group, which may overestimate treatment effect.[32] Interpretation is also limited by the relatively small sample size in P2 and P3. To allow comparison of time-to-flare data from the EMBARK study, the 2 studies were similar for inclusion and exclusion criteria; however, this may limit generalizability given that participants in RE-EMBARK represent a selected clinical trial population. Supporting the cross-study comparison with EMBARK, patient demographics and baseline disease characteristics were generally similar between the studies, although more patients in EMBARK were Asian, likely because of differences in study locations. Only those patients in EMBARK who met the entry requirements specified for the withdrawal period of the RE-EMBARK study were included in this analysis. Another limitation was using ASDAS-CRP to define inactive disease and ASDAS-ESR to define flare, for practical reasons; although these measures are clinically comparable, they are not identical. The ASDAS-ESR, however, serves as an identifier of flare/disease activity relapse. In addition, RE-EMBARK did not investigate dose reductions or changing the dosing interval, although tapering treatment is recommended for some patients.[2-4] Data from the randomized controlled C-OPTIMISE study[26] as well as open-label[33,34] and observational[35-38] studies of TNFi suggest that dose tapering is an effective way of controlling axSpA in some patients and that such tapering is noninferior to full dose. Longitudinal axial MRI and radiographic data were not collected, so the effect of ETN withdrawal on irreversible structural damage could not be assessed. In addition, it was not necessary for patients in P1 to have sustained inactive disease at week 24 (ie, over > 1 study visit) to enter P2. As patients in RE-EMBARK were retreated with ETN after 1 flare, the study also did not address the potential effect of ETN retreatment in patients with more than 1 flare after ETN withdrawal. Finally, the analysis of baseline predictors of maintaining inactive disease after ETN withdrawal and regaining inactive disease upon retreatment was post hoc in nature.

In conclusion, whereas most patients with nr-axSpA who achieved inactive disease with ETN flared after ETN withdrawal, a quarter of the patients did not experience ASDAS flare for 40 weeks despite treatment discontinuation. While this is an encouraging outcome for early aggressive treatment with a TNFi in patients with nr-axSpA, further studies with longer follow-up are needed.

DATA AVAILABILTY

The RE-EMBARK clinical trial protocol is available at https://clinicaltrials.gov/ProvidedDocs/26/NCT02509026/Prot_001.pdf. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

ACKNOWLEDGMENT

The authors wish to thank all patients and study investigators who participated in the RE-EMBARK study. Medical writing support was provided by Lorna Forse, PhD, and Iain McDonald, PhD, of Engage Scientific Solutions, and was funded by Pfizer. Some of the data in this manuscript were previously presented at the 2020 virtual European Alliance of Associations for Rheumatology Congress as an oral presentation (abstract number: OP0107[39]).

PLAIN LANGUAGE SUMMARY

A plain language summary of this article is included as online supplementary material.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Isdale A, Keat A, Barkham N, et al. Expanding the spectrum of inflammatory spinal disease: AS it was, as it is now. Rheumatology 2013;52:2103-5.
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;76:978-91.
3. Tam LS, Wei JCC, Aggarwal A, et al. 2018 APLAR axial spondyloarthritis treatment recommendations. Int J Rheum Dis 2019;22:340-56.
4. 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;71:1599-613.
5. 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;68:282-98.
6. Dougados M, van der Heijde D, Sieper J, et al. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol 2014;66:2091-102.
7. Maksymowych WP, Dougados M, van der Heijde D, et al. Clinical and MRI responses to etanercept in early non-radiographic axial spondyloarthritis: 48-week results from the EMBARK study. Ann Rheum Dis 2016;75:1328-35.
8. Dougados M, van der Heijde D, Sieper J, et al. Effects of long-term etanercept treatment on clinical outcomes and objective signs of inflammation in early nonradiographic axial spondyloarthritis: 104-week results from a randomized, placebo-controlled study. Arthritis Care Res 2017;69:1590-8.
9. López-Medina C, Ramiro S, van der Heijde D, Sieper J, Dougados M, Molto A. Characteristics and burden of disease in patients with radiographic and non-radiographic axial spondyloarthritis: a comparison by systematic literature review and meta-analysis. RMD Open 2019;5:e001108.
10. Song IH, Althoff CE, Haibel H, et al. Frequency and duration of drug-free remission after 1 year of treatment with etanercept versus sulfasalazine in early axial spondyloarthritis: 2 year data of the ESTHER trial. Ann Rheum Dis 2012;71:1212-5.
11. Siegfried EC, Eichenfield LF, Paller AS, Pariser D, Creamer K, Kricorian G. Intermittent etanercept therapy in pediatric patients with psoriasis. J Am Acad Dermatol 2010;63:769-74.
12. Yahya F, Gaffney K, Hamilton L, et al. Tumour necrosis factor inhibitor survival and predictors of response in axial spondyloarthritis-findings from a United Kingdom cohort. Rheumatology 2018;57:619-24.
13. Deodhar A, Yu D. Switching tumor necrosis factor inhibitors in the treatment of axial spondyloarthritis. Semin Arthritis Rheum 2017;47:343-50.
14. Macfarlane GJ, Pathan E, Jones GT, Dean LE. Predicting response to anti-TNFα therapy among patients with axial spondyloarthritis (axSpA): results from BSRBR-AS. Rheumatology 2020;59:2481-90.
15. Zurita Prada PA, Urrego Laurin CL, Guillen Astete CA, Kanaffo Caltelblanco S, Navarro-Compan V. Influence of smoking and obesity on treatment response in patients with axial spondyloarthritis: a systematic literature review. Clin Rheumatol 2021;40:1673-86.
16. Maksymowych WP, Kumke T, Auteri SE, Hoepken B, Bauer L, Rudwaleit M. Predictors of long-term clinical response in patients with non-radiographic axial spondyloarthritis receiving certolizumab pegol. Arthritis Res Ther 2021;23:274.
17. Sieper J, Landewe R, Magrey M, et al. Predictors of remission in patients with non-radiographic axial spondyloarthritis receiving open-label adalimumab in the ABILITY-3 study. RMD Open 2019;5:e000917.
18. Coates LC, Abraham S, Tillett W, et al. Performance and predictors of minimal disease activity response in patients with peripheral spondyloarthritis treated with adalimumab. Arthritis Care Res 2022;74:259-67.
19. Lorenzin M, Ortolan A, Frallonardo P, Oliviero F, Punzi L, Ramonda R. Predictors of response and drug survival in ankylosing spondylitis patients treated with infliximab. BMC Musculoskelet Disord 2015;16:166.
20. Lin Z, Liao Z, Huang J, et al. Predictive factors of clinical response of infliximab therapy in active nonradiographic axial spondyloarthritis patients. Biomed Res Int 2015;2015:876040.
21. Brown MA, Bird PA, Robinson PC, et al. Evaluation of the effect of baseline MRI sacroiliitis and C reactive protein status on etanercept treatment response in non-radiographic axial spondyloarthritis: a post hoc analysis of the EMBARK study. Ann Rheum Dis 2018;77:1091-3.
22. Lian F, Zhou J, Wang Y, Chen D, Xu H, Liang L. Efficiency of dose reduction strategy of etanercept in patients with axial spondyloarthritis. Clin Exp Rheumatol 2018;36:884-90.
23. 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.
24. Moreno M, Gratacos J, Torrente-Segarra V, et al. Withdrawal of infliximab therapy in ankylosing spondylitis in persistent clinical remission, results from the REMINEA study. Arthritis Res Ther 2019;21:88.
25. Landewé R, Sieper J, Mease P, et al. Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. Lancet 2018;392:134-44.
26. Landewé RB, van der Heijde D, Dougados M, et al. Maintenance of clinical remission in early axial spondyloarthritis following certolizumab pegol dose reduction. Ann Rheum Dis 2020;79:920-8.
27. Landewe RB, Gensler LS, Poddubnyy D, et al. Continuing versus withdrawing ixekizumab treatment in patients with axial spondyloarthritis who achieved remission: efficacy and safety results from a placebo-controlled, randomised withdrawal study (COAST-Y). Ann Rheum Dis 2021;80:1022-30.
28. Arends S, Brouwer E, van der Veer E, et al. Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. Arthritis Res Ther 2011;13:R94.
29. Rudwaleit M, Claudepierre P, Wordsworth P, et al. Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. J Rheumatol 2009;36:801-8.
30. Rusman T, van Bentum RE, van der Horst-Bruinsma IE. Sex and gender differences in axial spondyloarthritis: myths and truths. Rheumatology 2020;59:iv38-46.
31. Kilic G, Kilic E, Ozgocmen S. Is there any gender-specific difference in the cut-off values of ankylosing spondylitis disease activity score in patients with axial spondyloarthritis? Int J Rheum Dis 2017;20:1201-11.
32. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408-12.
33. De Stefano R, Frati E, De Quattro D, Menza L, Manganelli S. Low doses of etanercept can be effective to maintain remission in ankylosing spondylitis patients. Clin Rheumatol 2014;33:707-11.
34. Gratacos J, Pontes C, Juanola X, et al. Non-inferiority of dose reduction versus standard dosing of TNF-inhibitors in axial spondyloarthritis. Arthritis Res Ther 2019;21:11.
35. Almirall M, Salman TC, Lisbona MP, Maymó J. AB0671 dosage reduction of biological therapy in patients with axial spondyloarthritis in persistent clinical remission [abstract]. Ann Rheum Dis 2014;73:1027.

36. Arends S, van der Veer E, Kamps FBS, et al. Patient-tailored dose reduction of TNF-alpha blocking agents in ankylosing spondylitis patients with stable low disease activity in daily clinical practice. Clin Exp Rheumatol 2015;33:174-80.
37. Park JW, Kwon HM, Park JK, et al. Impact of dose tapering of tumor necrosis factor inhibitor on radiographic progression in ankylosing spondylitis. PLoS One 2016;11:e0168958.
38. 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.
39. Van den Bosch F, Wei JCC, Nash P, et al. OP0107 etanercept withdrawal and re-treatment in patients with inactive non-radiographic axial spondyloarthritis at 24 weeks: results of RE-EMBARK, an open-label, phase IV trial [abstract]. Ann Rheum Dis 2020;79:70.