REVIEW ARTICLE

Pharmacokinetics, efficacy and safety profiles of etanercept monotherapy in Japanese patients with rheumatoid arthritis: review of seven clinical trials

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Abstract

Conventional synthetic disease-modifying anti-rheumatic drugs, including methotrexate, may not be tolerated by all patients with rheumatoid arthritis (RA), and limited international data for etanercept (ETN) monotherapy are available. The aim of this review was to summarize the clinical program for ETN monotherapy in Japanese patients with RA, which has included a pharmacokinetic study, clinical trials for registration, long-term studies, and once-weekly dosing studies. Pharmacokinetic results showed that serum concentrations of ETN were linear with dose levels and were similar to other international studies. Across interventional studies, 652 Japanese patients with active RA were treated with ETN. In the registration studies, ETN treatment led to consistent improvement in American College of Rheumatology 20/50/70 scores, European League Against Rheumatism Good Response, Disease Activity Score 28 erythrocyte sedimentation rate remission, and Health Assessment Questionnaire disability index. In the long-term studies, efficacy was maintained for up to 180 weeks. Similar results were seen in the once-weekly studies. Across the studies, more than 870 patient-years of exposure to ETN were recorded. Discontinuations owing to lack of efficacy or adverse events were modest and no new safety signals were recorded. These studies demonstrated that ETN monotherapy is efficacious and well-tolerated in Japanese patients with RA.

Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory rheumatic disease that, without effective management, could lead to joint destruction and functional impairment. Its prevalence in Japan is up to 1.0% and in the global population is 0.5–1.0%, with higher occurrence in women [1,2]. New treatment strategies, particularly tumor necrosis factor (TNF) antagonists, have provided historically unprecedented outcomes for RA and made clinical remission an achievable target [3,4]. Etanercept (ETN), a fully human fusion TNF soluble receptor, inhibits the effect of the proinflammatory cytokine TNF-α, which plays an important role in synovitis and joint damage in RA.

ETN has been approved for the treatment of RA in Japan since 2005, and the approved indication was revised to include the prevention of joint destruction in 2012 by the Ministry of Health, Labor and Welfare [5,6]. The recommended dosages and administration of ETN are 10–25 mg twice weekly (BIW) or 25–50 mg once weekly (QW) for adults with active RA. Contraindications for ETN include ongoing infection, history of serious infection in the recent 6 months, history of tuberculosis, *Pneumocystis carinii* pneumonia (PCP), and congestive heart failure.

The approval of ETN for the treatment of RA in Japan was based on clinical trial data in Japanese patients with the results of pivotal studies from Europe and the United States [7–10]. There has been a large clinical development program to study efficacy, radiographic, and safety outcomes in Japanese patients with RA. The studies enrolled more than 800 participants (> 870 patient-years of exposure to ETN) and included pharmacokinetic studies, registrational studies, long-term efficacy, and safety studies, as well as QW dose regimen studies. The data from these studies will inform rheumatologists about the clinical utility of ETN in Japanese patients with RA.

The rationale for this review was the need for a comprehensive overview of primary clinical trials that examine the treatment of RA with ETN in the Japanese population. The objective was to examine the efficacy and safety of ETN monotherapy across multiple clinical studies and to inform clinical professionals on the clinical value of ETN monotherapy in the treatment of RA in Japan.

Materials and methods

Studies

The studies chosen for this review were conducted by Pfizer Inc/Wyeth in patients living in Japan and of Japanese descent

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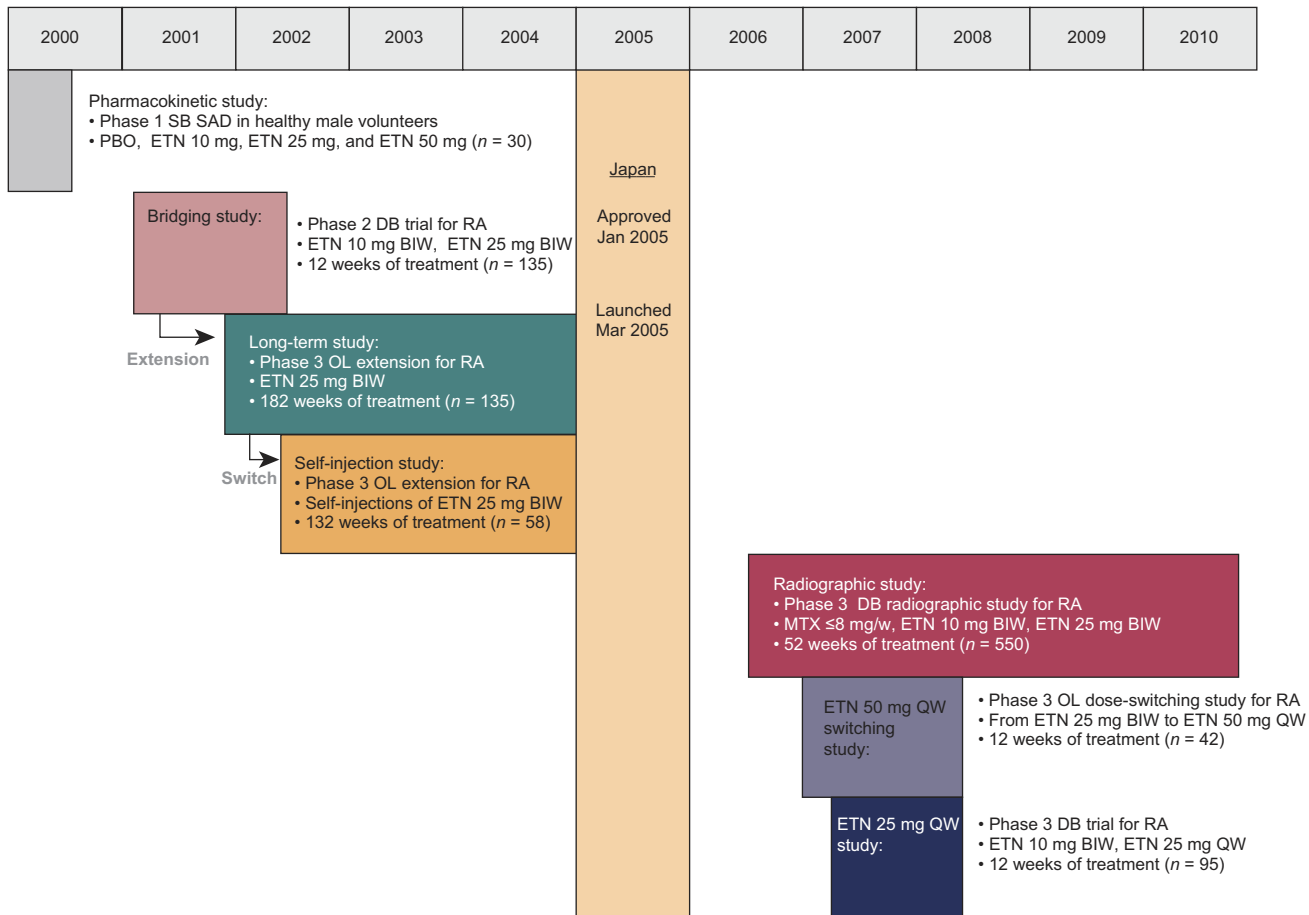
Figure 1. Overview of the Japanese clinical development program and the studies included in this review. *SB* single blind; *SAD* single ascending dose; *PBO* placebo; *ETN* etanercept; *DB* double blind; *RA* rheumatoid arthritis; *BIW* twice weekly; *OL* open-label; *MTX* methotrexate; *QW* once weekly.

(Figure 1, Table 1). The clinical studies examined in this overview included a Phase 1 single-dose pharmacokinetic study in healthy male volunteers (pharmacokinetic study), a Phase 2 double-blind placebo-controlled bridging study evaluating ETN 10- and 25-mg BIW for 12 weeks (bridging study), and a Phase 3 double-blind radiographic study comparing ETN 10-mg and ETN 25-mg BIW with up to 8 mg of methotrexate (MTX) weekly for 52 weeks (radiographic study). The bridging study was followed by two phase 3 open-label long-term extension studies (a long-term extension study featuring clinician-administered injections and a self-injection extension study). Alternative ETN dosing regimens were examined in 2 phase 3 QW dose studies: a 50 mg QW switching regimen study (50 mg QW switching study) and a 25 mg QW dose-regimen study (25 mg QW study).

Study protocols and key procedures

All study protocols were reviewed and approved by the Ministry of Health, Labor and Welfare of Japan and by the institutional review board of each study site. All patients provided written informed consent.

Pharmacokinetic protocols and procedures

The pharmacokinetics of ETN were estimated in the pharmacokinetic, bridging, radiographic, and 50 mg QW switching studies. Serum ETN concentrations were determined using a validated enzyme-linked immunosorbent assay with a lower limit of quantification of 0.39 ng/mL. In the pharmacokinetic study, healthy male Japanese volunteers received either a single dose of placebo or ETN 10 mg, ETN 25 mg, or ETN 50 mg subcutaneously. During this study, serial blood samples for ETN concentration measurement were collected before administration and up to 480 h after injection. Urine collections for ETN concentration measurement were made before administration and up to 72 h after injection. During the multiple dose studies, serum samples for trough ETN concentrations were collected at Weeks 4, 8, and 12 for the bridging study and Weeks 12, 24, and 52 for the radiographic study. A subset of 18 patients in the 50 mg QW switching study participated in pharmacokinetic assessments after receiving the ETN 25-mg BIW (Week 4) and ETN 50-mg QW (Week 12) dose regimens. Serum samples were collected on Day 0 (pre-dose) and every day thereafter for 7 days during Weeks 4 (ETN 25-mg BIW) and 12 (ETN 50-mg QW).

Efficacy and safety protocols and procedures

Efficacy was examined in the bridging, radiographic, long-term, self-injection, 50 mg QW switching, and 25 mg QW studies. In these studies, all patients had an inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (conventional synthetic DMARDs), and went through a wash-out period for their DMARD treatments prior to the start of the study. Patients received either ETN 10-mg BIW, ETN 25-mg BIW, ETN 25-mg QW, or ETN 50-mg QW monotherapy for at least 4 weeks (concomitant use of synthetic DMARDs, including MTX, were not permitted); comparator treatments were either placebo or MTX. The bridging study was a 12-week, randomized, double-blind, multicenter, dose–response study evaluating the safety and efficacy of placebo, ETN 10-mg BIW, and ETN 25-mg BIW. The radiographic study had a similar dosing schedule for ETN and included

Table 1. Summary of clinical studies.

Study	Pharmacokinetic	Registrational		Extension		ETN QW dose regimen	
		Bridging	Radiographic	Long-term	Self-injection	ETN 50-mg QW switching	ETN 25-mg QW
Participants	Healthy male	Active RA who have inadequate response to at least one conventional synthetic DMARD (DMARD-IR)	Active RA who have inadequate response to at least one conventional synthetic DMARD (DMARD-IR)	Patient who participated in bridging study	Patients who participated in long-term study	Patients with stable disease activity who received ETN 25 mg BIW for 6 mo in PMS	Active RA who have inadequate response to at least one conventional synthetic DMARD (DMARD-IR)
n	30	147	550	135	58	42	95
Design	DBT, SAD	DBT	DBT	Open	Open	Open-dose switching	DBT
No. of SJC and TJC at BL	NA	SJC: ≥ 6 TJC: ≥ 12	SJC:≥ 6 TJC: ≥ 6	NA	NA	NA	SJC: ≥ 6 TJC: ≥ 6
Treatment groups	Placebo SC ETN 10 mg SC ETN 25 mg SC ETN 50 mg SC	Placebo ETN 10 mg BIW SC ETN 25 mg BIW SC	MTX (≤ 8 mg/wk) oral ETN 10-mg BIW SC ETN 25-mg BIW SC	ETN 25 mg BIW SC	ETN 25-mg BIW SC	ETN 25-mg BIW SC switch to ETN 50 mg QW SC	ETN 10-mg BIW SC ETN 25-mg QW SC
Treatment duration	Single dose	12 wk	52 wk	Until approval (max 182 wk)	Until approval (max 132 wk)	12 wk (ETN 25 mg BIW for 4 wk followed by ETN 50 mg QW for 8 wk)	12 wk
Primary efficacy assessment	NA	ACR20 response rate at wk 12	Change of mTSS from baseline at wk 52	ACR response rates over time	ACR response rates over time	Difference of change from BL for DAS28 ESR at wk 4 and 12	Difference of change from BL for DAS28 ESR between 10 mg BIW and 25 mg QW at wk 12
Safety assessment	Medical history, monitoring of AEs, vital signs (in the sitting position), body weight, height, complete physical examination, CXR, 12-lead ECG, HBsAg and Ab to HCV, blood chemistry, hematology, and urinalysis, and serum and urine HCG for women of childbearing potential (excluding PK study). Particular attention given to infections.						
PK sampling	Intensive	Trough	Trough	NA	NA	Intensive (sub-study, n = 18)	Trough
Immunogenicity	NA	Anti-ETN Ab Neutralizing Ab	NA	Anti-ETN Ab Neutralizing Ab	Anti-ETN Ab Neutralizing Ab	NA	NA

PK pharmacokinetic; *ETN* etanercept; *QW* once weekly; *DMARD-IR* patients with active RA who had inadequate response to ≥ 1 disease modifying anti-rheumatic drug; *BIW* twice weekly; *PMS* post-marketing surveillance; *DBT* double-blind trial; *SAD* single ascending dose; *SJC* swollen joint count; *TJC* tender joint count; *BL* baseline; *NA* not applicable; *SC* subcutaneous; *MTX* methotrexate; *ACR* American College of Rheumatology; *mTSS* modified total Sharp score; *DAS28 ESR* Disease Activity Score in 28 joints; *AE* adverse event; *CXR* chest x-ray; *ECG* electrocardiogram; *HBsA* hepatitis B surface antigen; *Ab* antibody; *HCV* hepatitis C virus; *HCG* human chorionic gonadotropin.

an MTX treatment arm (up to 8 mg weekly); this study was 52 weeks long and measured radiographic outcomes in addition to safety and clinical outcomes. Patients in the long-term and self-injection studies received ETN 25-mg BIW and were 182 weeks and 132 weeks in length, respectively. The 25-mg QW study was a Phase 3, double-blind, multicenter, parallel study that compared ETN 10-mg BIW and ETN 25-mg QW over 12 weeks. The 50-mg QW switching study was a Phase 3, open-label, multicenter, dose-regimen trial in patients who had received commercial ETN for at least 6 months; during this 12-week study, patients were administered ETN 25-mg BIW for 4 weeks followed by ETN 50-mg QW for 8 weeks. Clinical responses were recorded at each visit and included American College of Rheumatology (ACR) response criteria, Disease Activity Score in 28 joints (DAS28 ESR), and European League against Rheumatism (EULAR) Good Response criteria based on the DAS28. In the radiographic study, radiographic outcomes also were assessed using modified total Sharp score (mTSS) at 52 weeks of treatment with ETN 10-mg BIW, ETN 25-mg BIW, and MTX up to 8 mg weekly. New remission criteria [Boolean remission and simplified disease activity index (SDAI) remission] were examined in post hoc analyses where applicable data were available. Functional disability was assessed by patient-reported outcomes using the validated Japanese version of the Health Assessment Questionnaire disability index (HAQ-DI).

Standard safety assessments were performed in all studies and are reported herein for the six efficacy studies. Adverse events including clinically meaningful abnormality of laboratory tests and vital signs were evaluated. Adverse events in the bridging, long-term, and self-injection studies were re-coded for this overview using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0. The radiographic study used the MedDRA version 13.0 and the 25-mg QW and 50-mg QW switching studies used the MedDRA version 10.1.

Safety data for the three sequential (bridging, long-term, and self-injection) studies were pooled for analyses of adverse events. Kaplan–Meier plots displaying time to withdrawal by reasons of adverse events, lack of efficacy, or other were produced. In addition, data on adverse events were summarized as an incidence rate by percentage and per 100 patient-years.

Immunogenicity (anti-ETN antibody and neutralizing antibody) was assessed in the three sequential (bridging, long-term, and self-injection) studies using a validated enzyme-linked immunosorbent assay.

Statistical methods

The clinical efficacy analysis data for the bridging, long-term, self-injection, radiographic, 25-mg QW, and 50-mg QW switching studies included all randomized and treated patients, except for six patients in the bridging study who were excluded owing to a violation of good clinical practice that may have occurred. Data for the bridging, radiographic, and 25-mg QW studies included last observation carried forward imputation for missing data. Observed data are presented for the long-term, self-injection, and 50 mg QW switching studies. Efficacy data for Weeks 169 and 182 in the long-term study and Week 132 in the self-injection study were censored owing to very low population sizes that confounded interpretation. Safety analyses were performed for all randomized patients who received at least one dose of study drug.

Descriptive statistics were used to summarize change from baseline in the DAS28 ESR, HAQ-DI, ACR components, and the proportions of patients who achieved remission (DAS28 ESR, SDAI, or Boolean remission) and normal HAQ-DI (≤ 0.5).

Results

Pharmacokinetics

Pharmacokinetic study

In the Phase 1 pharmacokinetic study, the pharmacokinetics of ETN were linear in the dose range administered (Supplementary Figure 1a, Supplementary Table 1 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014) [11]. The mean maximum serum concentration (C_{max}) and mean area under the curve (AUC) were proportional to the dose of ETN. After a single subcutaneous administration in healthy volunteers, ETN 25-mg was absorbed slowly, reaching a C_{max} of 1.37 ± 0.72 μg/mL at 47 ± 15 h, with the AUC being 217 ± 85.7 μg.h/mL. ETN was slowly eliminated from the body at the half-life of 80 ± 25 h. Urinary excretion of this drug was not observed.

Bridging and radiographic studies

The pharmacokinetics of ETN were also studied in the bridging and radiographic studies. In the bridging study, mean ETN serum concentration (trough) remained virtually constant over a 12-week period (Supplementary Table 2 available online at http://informa healthcare.com/doi/abs/10.3109/14397595.2014.914014). The serum concentration was found to reach steady-state after a month of repeated administration and was about twice the highest concentration after a single administration, showing no accumulation exceeding the predicted concentration. The mean serum concentrations (trough) of ETN in the radiographic study were comparable to those of the bridging study after 12 weeks of treatment at both doses (Supplementary Tables 2 and 3 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014). The mean ETN serum concentration in the radiographic study remained virtually constant at all time points for up to Week 52 in both the ETN 10-mg BIW and ETN 25-mg BIW treatment groups and was nearly proportional to the dose (Supplementary Table 3 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014).

50-mg QW switching and 25-mg QW studies

The 50-mg QW switching study, in which patients already receiving ETN were switched from a 25-mg BIW to a 50-mg QW dosing regimen, included a pharmacokinetic component ($n = 18$) to examine QW dosing. The steady-state concentrations for the two dosing regimens generally overlapped (mean [standard deviation (SD)] C_{max} for ETN 25-mg BIW at Week 4 was 3.5 (1.1) μg/mL and 3.7 (1.3) μg/mL for ETN 50-mg QW at Week 12). Steady-state weekly exposure (AUC) and mean serum concentration of ETN also were comparable between the 25-mg BIW (mean [SD]: 19.7 [5.7] μg $\times$ day/mL and 2.8 [0.8] μg/mL) and the 50-mg QW (mean [SD]: 17.9 [6.1] μg $\times$ day/mL and 2.6 [0.9] μg/mL) regimens (Supplementary Figure 1b, Supplementary Table 4 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014).

Patient characteristics

Bridging and radiographic studies

The mean ages of patients in the bridging and radiographic studies were 53 and 51 years, respectively; the majority of patients in each study were female (86% and 80%, respectively; Table 2). The majority of the baseline disease characteristics (i.e., DAS28 erythrocyte sedimentation rate [ESR], physician's global assessment, pain visual analogue scale, HAQ-DI) were similar for the two studies; however, patients in the radiographic study had shorter disease duration (3 years), lower percent of rheumatoid factor-positive

Table 2. Baseline demographics and disease characteristics in the registrational and ETN QW dosing regimen studies.

	Registrational		ETN QW dosing regimen	
	Bridging N = 147	Radiographic N = 550	50-mg QW switching N = 42	25-mg QW N = 95
Age, y	52.6 (11.6)	51.2 (11.7)	53.1 (13.2)	54.7 (10.5)
Sex, *n* (%)				
Male	21 (14.3)	111 (20.2)	7 (16.7)	10 (10.5)
Female	126 (85.7)	439 (79.8)	35 (83.3)	85 (89.5)
Disease duration, y	11.0 (9.3)	3.0 (2.7)	10.9 (8.2)	8.3 (6.9)
RF positive, *n* (%)	136 (92.5)	422 (76.7)	–	–
CRP, mg/dL	4.9 (3.3)	2.2 (2.6)	0.2 (0.4)	3.4 (2.8)
ESR, mm/hr	72.7 (30.1)	42.7 (28.4)	24.0 (16.8)	64.8 (32.3)
DAS28 ESR	7.1 (0.9)	5.8 (1.1)	3.2 (0.4)	6.4 (1.0)
Tender joint count	28.0 (13.4)	10.4 (6.1)[a]	1.9 (2.1)[a]	11.6 (6.6)[a]
Swollen joint count	22.4 (11.2)	9.5 (5.3)[a]	1.7 (2.1)[a]	10.9 (5.8)[a]
Physician global assessment[b]	67.3 (17.1)	6.3 (1.9)	2.1 (1.1)	6.7 (2.0)
Patient global assessment[b]	67.8 (18.1)	6.0 (2.2)	2.9 (1.4)	6.7 (2.1)
Pain VAS score	65.3 (17.6)	54.0 (22.8)	21.5 (13.6)	60.2 (21.3)
HAQ-DI	1.7 (0.6)	1.1 (0.7)	0.6 (0.6)	1.4 (0.6)
Duration of morning stiffness, min	4.2 (6.6)	210.6 (328.9)	11.1 (17.0)	154.2 (191.1)
mTSS	–	43.4 (42.3)	–	–
Annualized mTSS progression rate	–	28.2 (40.5)	–	–
Erosion score	–	25.7 (24.1)	–	–
Joint space narrowing score	–	17.7 (20.0)	–	–
Prior MTX use	127 (86.4)	352 (64.0)	29 (69.0)	60 (63.2)

ETN etanercept; *QW* once weekly; *RF* rheumatoid factor; *CRP* C-reactive protein; *ESR*, erythrocyte sedimentation rate; *DAS28 ESR* Disease Activity Score in 28 joints; *VAS* visual analogue scale; *HAQ-DI* Health Assessment Questionnaire disability index; *mTSS*, modified total Sharp score.
Values are mean (standard deviation) unless otherwise noted.
[a]Based on 28 joints; [b]The bridging study used a 100-mm scale whereas the radiographic, 50-mg QW switching, and 25 QW studies used a 10-mm scale.

patients, lower mean ESR, lower swollen and tender joint counts, and longer duration of morning stiffness relative to the bridging study. The baseline mean mTSS and mTSS annualized rate of progression in the radiographic study were 43.4 and 28.2, respectively (Table 2). The long-term and self-injection studies were open-label extensions of the bridging study.

50-mg QW switching and 25-mg QW studies

The mean age and percentage of female patients in the 50-mg QW switching and 25-mg QW studies were 53 and 55, 83% and 90%, respectively (Table 2), and consistent with those of the registrational studies. Disease duration also was consistent (10.9 and 8.3 years, respectively). Patients in the 25-mg QW study had baseline disease characteristics that were generally consistent with those patients in the registrational studies. Patients in the 50-mg QW switching study had been receiving ETN treatment at baseline and had lower serum C-reactive protein (CRP), ESR, tender and swollen joint counts, and pain assessment.

Efficacy

Bridging and radiographic studies

The efficacy data in the two registrational (bridging and radiographic) studies showed early and consistent improvement across multiple clinical and radiographic outcomes. Improvements in ACR20, 50, and 70 response rates and mean changes in DAS28 ESR scores over placebo in the bridging study and over MTX in the radiographic study were apparent in both ETN treatment groups by Week 4 and continued to improve with treatment (Figure 2a and b, Figure 3a and b). In the bridging study, ACR20 response at Week 12 was significantly less in the placebo group (6.3%) than in the ETN 10-mg BIW group (64.0%) and the ETN 25-mg BIW group (65%). In the radiographic study, ACR20 for MTX at Week 52 (62.5%), was significantly less than ETN

10-mg BIW (75.9%) and ETN 25-mg BIW (78.6%). Treatment with MTX in the radiographic study was less efficacious than treatment with the two ETN doses at every time point. Overall, the percentage of patients in the bridging and radiographic studies who achieved EULAR Good Response and DAS28 ESR remission (< 2.6) rose from Week 2 to the end of the studies (Supplementary Figures 3a, b and 4a, b available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014). In the bridging study, EULAR Good Response and DAS 28 remission rates were numerically higher with ETN 10-mg BIW and ETN 25-mg BIW than with placebo, but the differences were small and not statistically significant. In the longer-term radiographic study, EULAR Good Response at Week 52 in the MTX group (29.7%) was significantly less than that in the ETN 10-mg BIW (44.2%) and ETN 25-mg BIW (50.0%) groups; DAS28 ESR remission was achieved by 19.3% of patients in the MTX group, which was significantly less than that in the ETN 10-mg BIW (31.9%) and ETN 25-mg BIW (34.1%) groups. Significantly more patients achieved EULAR Good Response when treated with ETN 25-mg BIW (50%) than with ETN 10-mg BIW (44%, $P < 0.05$) [12]. Mean HAQ-DI scores decreased (improved) as early as Week 4 and continued to decrease over time in both the bridging and radiographic studies (Supplementary Figure 5a and b available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014). HAQ-DI scores improved by at least the minimum clinically important difference (0.3) in the bridging and radiographic studies from baseline to end of study. In the radiographic study, mean HAQ-DI scores approached the population norm of 0.5 or less by the end of study; improvements for both ETN dose groups were significantly greater compared with the respective comparators (placebo or MTX). The bridging and radiographic studies each recorded significant improvements in ESR and serum CRP between the baseline and end of study in patients treated with ETN. In the case of the bridging study, small differences observed between the low- and high-dose regimens did not reach statistical significance (Supplementary Table 5a
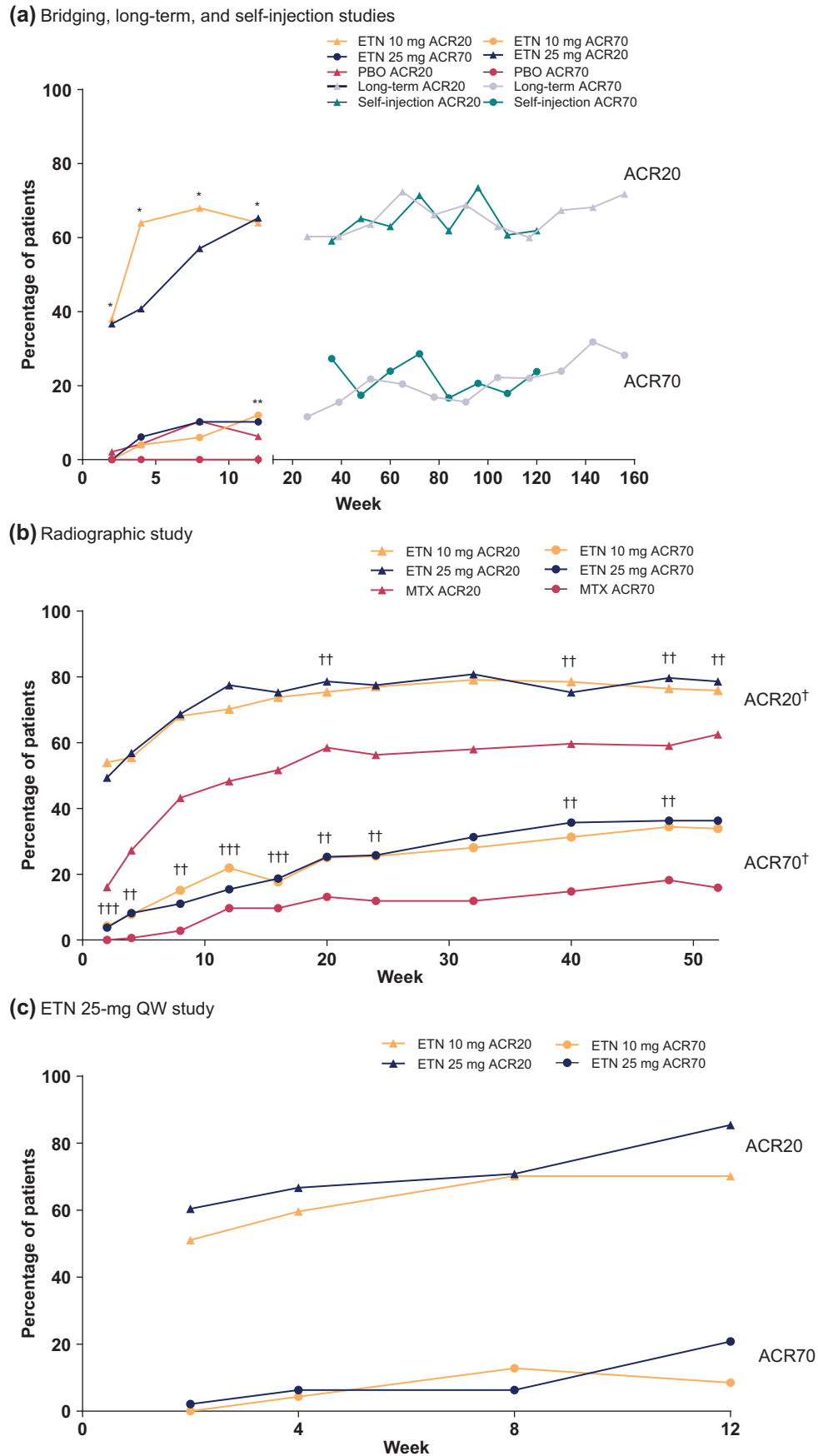
Figure 2. American College of Rheumatology (ACR) 20 and ACR70 responses over time. (a) Bridging (etancercept [ETN] 10 mg twice weekly [BIW], ETN 25-mg BIW, placebo [PBO]), long-term, and self-injection studies. (b) Radiographic study. (c) ETN 25 mg once weekly (QW) study. *$P < 0.001$ for both ETN 25-mg BIW and ETN 10-mg BIW versus PBO; **$P = 0.027$ for ETN 10-mg BIW versus PBO. †$P \leq 0.0001$ for ETN 10-mg BIW or ETN 25-mg BIW versus methotrexate (MTX) ≤ 8 mg/w at all points unless otherwise noted; ††$P \leq 0.01$ for ETN 10-mg BIW versus MTX ≤ 8 mg/w and ETN 25-mg BIW versus MTX ≤ 8 mg/w; †††$P \leq 0.05$ for ETN 10 mg BIW versus MTX ≤ 8 mg/w and ETN 25-mg BIW versus MTX ≤ 8 mg/w; $P = $ not significant for ETN 10-mg BIW ACR70 versus MTX ≤ 8 mg/w at Week 8.

available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014).

In the radiographic study, mean [SD] changes from baseline in mTSS at Week 52 in the ETN 10-mg BIW group (5.19 [0.93]) and the ETN 25-mg BIW group (3.33 [0.73]) were significantly smaller than in the MTX monotherapy group (9.82 [1.16]; Figure 4).[12]. Higher doses (25 mg BIW) of ETN resulted in less radiographic progression relative to lower doses of ETN (10-mg BIW) over 52 weeks (Figure 4) [12]. The mean change in joint space narrowing significantly favored ETN 25 mg BIW over ETN 10 mg BIW ($P = 0.0006$), and both ETN doses resulted in favorable joint space narrowing versus MTX ($P < 0.0001$).

Long-term and self-injection studies

ACR response rates, DAS28 ESR scores, EULAR Good Response, and DAS28 ESR remission rates observed at Week 12 in the bridging study were maintained in the open-label extension studies (≤ 160 weeks of treatment in the long-term study and ≤ 120 weeks in the self-injection study; Figure 2a, Supplementary Figures 2a, 3a and 4a available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014). Mean HAQ-DI scores continued to decrease (improve) or were maintained over time in each of the extension studies; the switch to self-injection during the self-injection study did not influence the efficacy response (Supplementary Figure 5a available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014). Overall, in other efficacy measures (i.e., SDAI and Boolean remission rates) CRP and ESR were maintained for the duration of the long-term and self-injection studies (Supplementary Table 5b and c available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014).

50-mg QW switching and 25-mg QW studies

In the 25-mg QW study, ETN 25-mg QW resulted in nominally, but not significantly, better responses for ACR20, 50, and 70 measures after 12 weeks of treatment compared with the ETN 10 mg BIW dose regimen (85% vs. 70%, 46% vs. 30%, 21% vs. 9%, respectively; Figure 2c, Supplementary Figure 2c available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014). Overall, the percentage of patients in the 25-mg QW study who achieved EULAR Good Response and DAS28 ESR remission (< 2.6) rose from Week 2 (ETN 25 mg QW 6% and 4%, ETN 10 mg BIW 4% and 2%, respectively) to the end of the study (ETN 25 mg QW 23% and 19%, ETN 10 mg BIW 23% and 9%, respectively; Supplementary Figures 3c and 4c available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014). Mean DAS28 ESR scores decreased (improved) from baseline during the 25-mg QW study (Figure 3c, Supplementary Table 5d available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014) as did mean HAQ-DI scores (ETN 25-mg QW -0.6, ETN 10-mg BIW -0.5; Supplementary Figure 5c available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014). Scores improved by at least the minimally clinically important difference (0.3) [13,14] between the baseline and end of study and approached the population norm of 0.5 or less [13,14] by end of study.

In the 50-mg QW switching study, improvements in DAS28 ESR were comparable after 4 weeks of treatment with ETN 25-mg BIW (Weeks 4–8) and 4 weeks with ETN 50-mg QW (Weeks 8–12; Supplementary Figure 6 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014). Mean DAS28 ESR scores indicated low disease activity (≤ 3.2) after 12 weeks of treatment.

Safety and immunogenicity

Radiographic study

Treatment-emergent adverse events and infections were generally similar in all three treatment arms (Table 3a). There were no major differences between the dose groups. Most TEAEs occurred at rates (events/100 patient-years) that were comparable to or less than the rates seen with MTX treatment (Table 3b). Similar results were seen with rates of infections (Table 3c). The most common treatment-emergent adverse events were increased liver enzymes, rash, eczema, and constipation. The most common treatment emergent infections were nasopharyngitis, upper respiratory tract infection, and pharyngitis. Withdrawals from the study owing to an adverse event included 9.3% of patients in the ETN 25-mg BIW group, 7.3% of patients in the ETN 10-mg BIW group, and 4.5% of patients in the MTX group; $\leq 2.1\%$ discontinued owing to infections (Table 3a). The rates of serious adverse events, serious infections, opportunistic infections, and malignancies were similar between the ETN treatment groups and the MTX group. The radiographic study had a low incidence of discontinuations, with the majority of patients remaining in the study until the end of the 52-week treatment period (Figure 5a, Supplementary Table 6 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014).

Pooled bridging, long-term, and self-injection studies

Patients in the bridging study had the option to enroll in the long-term or self-injection extension study. Thus, for a complete assessment of long-term safety, the adverse events data from these three studies were pooled. During these studies, more than 375 patient-years of exposure to ETN were recorded. One death was recorded during the bridging study (Table 3a); the cause was sepsis and the patient had been administered ETN 25-mg BIW. In the pooled studies, 16.3% and 11.6% of patients discontinued owing to adverse events and infections, respectively (Table 3a). We examined serious infections in the bridging and extension studies and found that during 375 patient-years of exposure, 14% of patients developed serious infections (7.5 events/100 patient-years), the most common of which was pneumonia (1.6 events/100 patient-years). No opportunistic infections (including tuberculosis and PCP) were observed during these studies (Table 3a). Consistent with the radiographic study, nasopharyngitis was the most common infection observed during long-term treatment with ETN (113 events/100 patient-years); other common infections (events/100 patient-years) over the long term included upper respiratory tract infection (23), cystitis (9), pharyngitis (5), periodontitis (5), conjunctivitis infective (4), bronchitis (3), herpes zoster (3), and tinea blanca (3; Table 3c).

The incidence of antibody development in patients treated with ETN was examined in the bridging study and subsequent extension studies. In the bridging study, anti-ETN antibodies were detected in 1/47 (2.1%) patients and 1/48 (2.1%) patients after 12 weeks of treatment in the ETN 10-mg BIW and ETN 25-mg BIW groups, respectively. In the long-term and self-injection studies, the incidence of anti-ETN antibodies varied from 2.1% to 10.6% at any given visit. None of the patients tested positive for neutralizing antibodies.

50-mg QW switching and 25-mg QW studies

No new safety signals were observed during the bridging once-weekly dosing studies (Supplementary Table 7 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.914014).
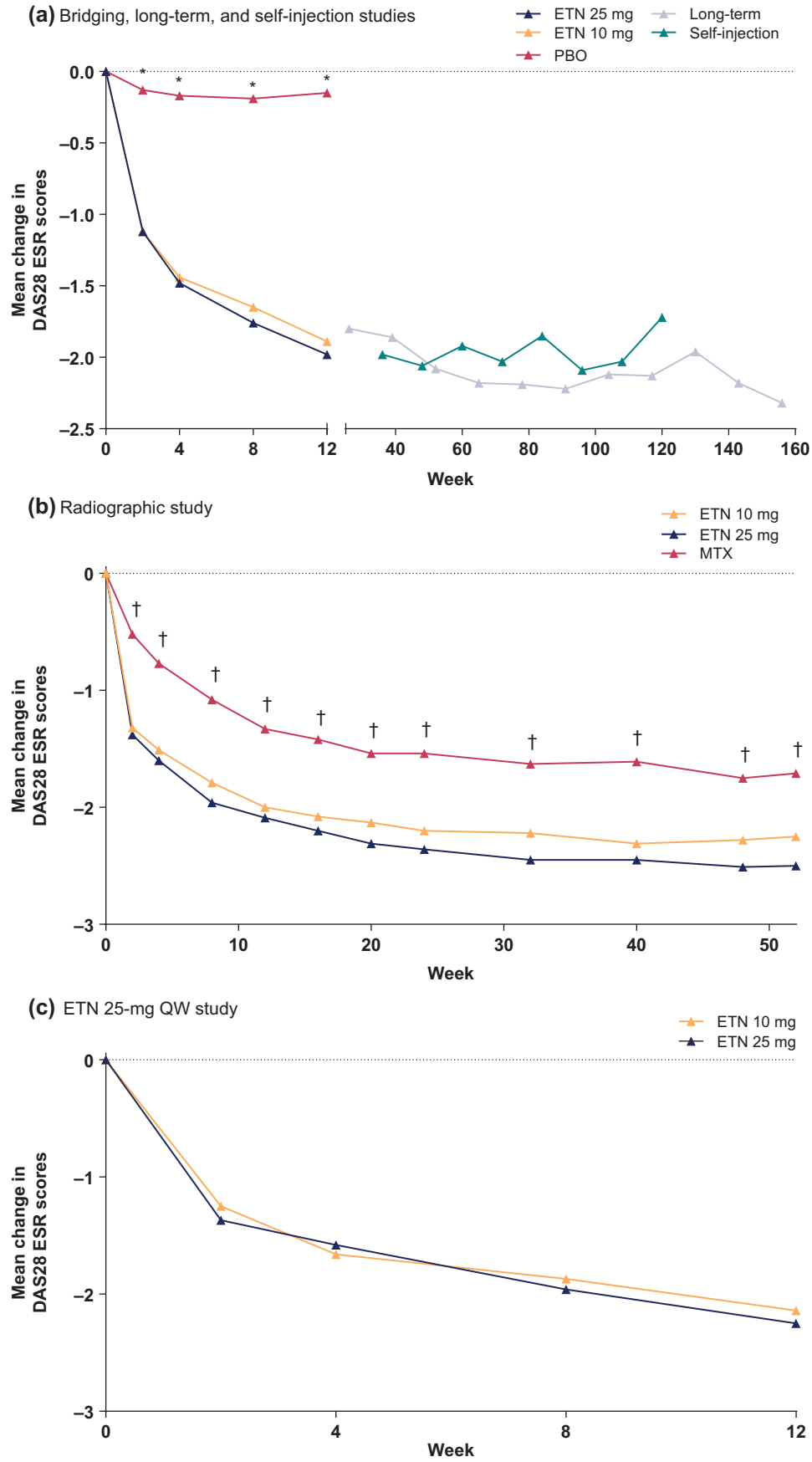
Figure 3. Mean changes in Disease Activity Index for 28 joints (DAS28 ESR) scores over time. (a) Bridging (etancercept [ETN] 10-mg twice weekly (BIW), ETN 25-mg BIW, placebo [PBO]), long-term, and self-injection studies. (b) Radiographic study. (c) ETN 25-mg once weekly (QW) study. *$P < 0.001$ for both ETN 25-mg BIW and ETN 10-mg BIW versus PBO. †$P \leq 0.0001$ for ETN 10-mg BIW or ETN 25-mg BIW versus methotrexate (MTX) ≤ 8 mg/w.

Table 3. Adverse events: (a) Overall adverse events; (b) Common adverse events; (c) Common infections.

(a) Overall adverse events (AEs).

	Pooled (bridging, long-term, and self- injection) studies[a]	Radiographic study[a]		
Treatment group	ETN 25-mg BIW[c]	ETN 10-mg BIW	ETN 25-mg BIW	MTX ≤ 8 mg/wk
No. of patients	N = 147	n = 192	n = 182	n = 176
Estimate exposure	Total exposure = 375.4 pt-y	Total exposure = 168.3 pt-y	Total exposure = 160.3 pt-y	Total exposure = 141.6 pt-y
Any TEAE,[b] n/N (%)	143 (97.3)	150 (78.1)	128 (70.3)	125 (71.0)
Death, n/N (%)	1	0	0	0
SAE,[b] n (%)	45 (30.6)	8 (4.2)	11 (6.0)	10 (5.7)
Discontinuation owing to AE, n (%)	24 (16.3)	14 (7.3)	17 (9.3)	8 (4.5)
Overall treatment-emergent infections, n/N (%)	124 (84.4)	106 (55.2)	102 (56.0)	92 (52.3)
Serious infections, n/N (%)	21 (14.3)	2 (1.0)	0	1 (0.6)
Discontinuation owing to infection, n/N (%)	17 (11.6)	4 (2.1)	3 (1.6)	1 (0.6)
Opportunistic infections, n/N (%)	0	0	0	0
TB, n/N (%), [events/100 pt-y]	0	0	0	0
PCP, n/N (%), [events/100 pt-y]	0	0	0	0
Hepatitis B, n/N (%) [events/100 pt-y]	0	0	0	0
Hepatitis C, n/N (%) [events/100 pt-y]	0	0	0	0
Overall treatment-emergent ISRs[d]	62 (42.2)	40 (20.8)	37 (20.3)	3 (1.7)
Malignancy, n (%) [events/100 pt-y]	2 (1.4) [0.53]	0	2 (1.1) [1.25]	2 (1.1) [1.41]
Other safety	4 (2.7)	0	0	0
IP, n/N (%) [events/100 pt-y]	4 (2.7) [1.07]	0	0	0
Demyelinating disorders, n/N (%) [events/100 pt-y]	0	0	0	0

ETN etanercept; *BIW* twice weekly; *Pt-y* patient years; *MTX* methotrexate; *TEAE* treatment-emergent adverse event; *SAE* serious adverse event; *TB* tuberculosis; *PCP* pneumocystis pneumonia; *ISR* injection site reaction; *IP* interstitial pneumonia.
[a]Medical Dictionary for Regulatory Activities version 13.0; [b]Excluding infections and ISRs; [c]102 patients received placebo or ETN 10-mg BIW for 12 weeks in the bridging study, then ETN 25-mg BIW after moving to the long-term study until initial drug approval in Japan; [d]Injection site reactions includes erythema, hematoma, pain, hemorrhage, pruritus, rash, and warmth.

Table 3. (b) Common adverse events (AEs).

	Pooled (bridging, long-term, and self-injection) studies[a]		Radiographic study[a]					
Treatment group	ETN 25-mg BIW		ETN 10-mg BIW		ETN 25-mg BIW		MTX ≤ 8 mg/wk	
No. of patients	N = 147		n = 192		n = 182		n = 176	
Estimate exposure	Total exposure = 375.4 pt-y		Total exposure = 168.3 pt-y		Total exposure = 160.3 pt-y		Total exposure = 141.6 pt-y	
AE	n (%)	Events/100 pt-y	n (%)	Events/100 pt-y	n (%)	Events/100 pt-y	n (%)	Events/100 pt-y
Rash	38 (25.9)	66 (17.58)	10 (5.2)	11 (6.536)	10 (5.5)	13 (8.110)	8 (4.5)	9 (6.357)
Eczema	27 (18.4)	49 (13.05)	7 (3.6)	8 (4.754)	8 (4.4)	10 (6.239)	8 (4.5)	9 (6.357)
Headache	32 (21.8)	48 (12.79)	5 (2.6)	5 (2.971)	9 (4.9)	15 (9.358)	4 (2.3)	5 (3.532)
Diarrhea	25 (17.0)	42 (11.19)	5 (2.6)	8 (4.754)	10 (5.5)	11 (6.862)	5 (2.8)	6 (4.238)
Pyrexia	18 (12.2)	45 (11.99)	2 (1.0)	3 (1.783)	9 (4.9)	11 (6.862)	6 (3.4)	7 (4.944)
Dizziness	25 (17.0)	37 (9.86)	7 (3.6)	7 (4.159)	3 (1.6)	4 (2.495)	1 (0.6)	1 (0.706)
Contusion	27 (18.4)	35 (9.32)	4 (2.1)	4 (2.377)	8 (4.4)	8 (4.991)	4 (2.3)	5 (3.532)
Pruritus	22 (15.0)	34 (9.06)	12 (6.3)	13 (7.724)	5 (2.7)	6 (3.743)	3 (1.7)	4 (2.825)
Nausea	18 (12.2)	27 (7.19)	4 (2.1)	4 (2.377)	1 (0.5)	1 (0.624)	7 (4.0)	8 (5.651)
Insomnia	19 (12.9)	24 (6.39)	9 (4.7)	9 (5.348)	2 (1.1)	2 (1.248)	9 (5.1)	9 (6.357)
Alanine aminotransferase increased	15 (10.2)	23 (6.13)	12 (6.3)	15 (8.913)	10 (5.5)	13 (8.110)	22 (12.5)	34 (24.015)
Cough	17 (11.6)	23 (6.13)	4 (2.1)	8 (4.754)	6 (3.3)	7 (4.367)	0	0
Vomiting	15 (10.2)	20 (5.33)	3 (1.6)	3 (1.783)	4 (2.2)	4 (2.495)	1 (0.6)	2 (1.413)
White blood cells urine positive	18 (12.2)	20 (5.33)	–	–	–	–	–	–
Injection site hemorrhage	15 (10.2)	21 (5.59)	2 (1.0)	4 (2.377)	2 (1.1)	2 (1.248)	0	0
Constipation	14 (9.5)	18 (4.80)	6 (3.1)	7 (4.159)	7 (3.8)	7 (4.367)	9 (5.1)	9 (6.357)
Stomatitis	13 (8.8)	18 (4.80)	8 (4.2)	8 (4.754)	3 (1.6)	3 (1.872)	8 (4.5)	12 (8.476)
Abdominal pain upper	15 (10.2)	17 (4.53)	3 (1.6)	3 (1.783)	3 (1.6)	3 (1.872)	5 (2.8)	5 (3.532)
Aspartate aminotransferase increased	9 (6.1)	16 (4.26)	8 (4.2)	11 (6.536)	8 (4.4)	11 (6.862)	18 (10.2)	25 (17.658)
Rhinitis allergic	9 (6.1)	10 (2.66)	6 (3.1)	6 (3.565)	1 (0.5)	1 (0.624)	3 (1.7)	4 (2.825)
Gastritis	8 (5.4)	8 (2.13)	3 (1.6)	3 (1.783)	1 (0.5)	1 (0.624)	6 (3.4)	8 (5.651)
Arthralgia	5 (3.4)	5 (1.33)	2 (1.0)	3 (1.783)	1 (0.5)	1 (0.624)	7 (4.0)	7 (4.944)
Abdominal discomfort	3 (2.0)	4 (1.07)	6 (3.1)	6 (3.565)	0	0	4 (2.3)	6 (4.238)
Transaminases increased	0	0	5 (2.6)	7 (4.159)	5 (2.7)	6 (3.743)	8 (4.5)	11 (7.770)
Hepatic function abnormal	0	0	5 (2.6)	5 (2.971)	3 (1.6)	4 (2.495)	6 (3.4)	9 (6.357)

ENT etanercept; *BIW* twice weekly; *Pt-y* patient years; *MTX* methotrexate.
[a]Medical Dictionary for Regulatory Activities version 13.0.

Table 3. (c) Common infections.

Treatment group No. of patients Estimate exposure	Pooled (bridging study, long-term, self-injection) studies[a] ETN 25-mg BIW $N = 147$ Total exposure = 375.4 pt-y		Radiographic study[a] ETN 10-mg BIW $n = 192$ Total exposure = 168.3 pt-y		ETN 25-mg BIW $n = 182$ Total exposure = 160.3 pt-y		MTX ≤ 8 mg/wk $n = 176$ Total exposure = 141.6 pt-y	
Type of infection	n (%)	Events/100 pt-y	n (%)	Events/100 pt-y	n (%)	Events/100 pt-y	n (%)	Events/100 pt-y
Nasopharyngitis	100 (68.0)	424 (113.0)	45 (23.4)	69 (41.0)	37 (20.3)	50 (31.2)	43 (24.4)	58 (41.0)
Upper respiratory tract infection	36 (24.5)	86 (22.9)	20 (10.4)	30 (17.83)	21 (11.5)	31 (19.3)	20 (11.4)	29 (20.4)
Cystitis	15 (10.2)	35 (9.3)	4 (2.1)	8 (4.8)	9 (4.9)	12 (7.5)	6 (3.4)	6 (4.2)
Pharyngitis	15 (10.2)	20 (5.3)	18 (9.4)	27 (16.0)	15 (8.2)	21 (13.1)	12 (6.8)	17 (12.0)
Periodontitis	11 (7.5)	18 (4.8)	1 (0.5)	1 (0.6)	5 (2.7)	5 (3.2)	0	0
Conjunctivitis infective	5 (3.4)	13 (3.5)	0	0	0	0	0	0
Bronchitis	11 (7.5)	12 (3.2)	5 (2.6)	6 (3.6)	6 (3.3)	6 (3.7)	5 (2.8)	7 (4.9)
Herpes zoster	11 (7.5)	11 (2.9)	3 (1.6)	3 (1.8)	3 (1.6)	4 (2.5)	1 (0.6)	1 (0.7)
Tinea blanca	11 (7.5)	11 (2.9)	0	0	0	0	0	0
Gastroenteritis	10 (6.8)	10 (2.7)	1 (0.5)	1 (0.6)	1 (0.5)	1 (0.6)	5 (2.8)	5 (3.5)
Dental caries	9 (6.1)	9 (2.4)	4 (2.1)	4 (2.4)	8 (4.4)	10 (6.2)	3 (1.7)	3 (2.1)
Influenza	7 (4.8)	9 (2.4)	4 (2.1)	4 (2.4)	1 (0.5)	1 (0.6)	6 (3.4)	6 (4.2)
Oral herpes	8 (5.4)	8 (2.1)	6 (3.1)	6 (3.6)	2 (1.1)	2 (1.2)	2 (1.1)	2 (1.4)
Nail infection	7 (4.8)	8 (2.1)	1 (0.5)	1 (0.6)	0	0	1 (0.6)	1 (0.7)
Hordeolum	5 (3.4)	7 (1.9)	2 (1.0)	2 (1.2)	4 (2.2)	4 (2.5)	1 (0.6)	1 (0.7)
Pneumonia	6 (4.1)	6 (1.6)	6 (3.1)	6 (3.6)	2 (1.1)	2 (1.2)	0	0
Herpes virus infection	5 (3.4)	6 (1.6)	1 (0.5)	1 (0.6)	0	0	0	0
Tinea pedis	6 (4.1)	6 (1.6)	1 (0.5)	1 (0.6)	0	0	0	0
Sinusitis	5 (3.4)	5 (1.3)	2 (1.0)	2 (1.2)	1 (0.5)	1 (0.6)	0	0
Onychomycosis	5 (3.4)	5 (1.3)	1 (0.5)	1 (0.6)	0	0	0	0
Gastroenteritis viral	3 (2.0)	4 (1.1)	0	0	0	0	0	0
Herpes simplex	2 (1.4)	4 (1.1)	0	0	0	0	0	0
Arthritis bacterial	3 (2.0)	4 (1.1)	0	0	0	0	0	0
Cough	4 (2.7)	4 (1.1)	1 (0.5)	1 (0.6)	0	0	0	0
Urinary tract infection	3 (2.0)	3 (0.8)	1 (0.5)	2 (1.2)	0	0	0	0
Cellulitis	2 (1.4)	2 (0.5)	3 (1.6)	3 (1.8)	1 (0.5)	3 (1.9)	0	0
Pyelonephritis	2 (1.4)	2 (0.5)	1 (0.5)	3 (1.8)	0	0	1 (0.6)	1 (0.7)
Tonsillitis	1 (0.7)	1 (0.3)	0	0	1 (0.5)	1 (0.6)	2 (1.1)	2 (1.4)
Paronychia	0	0	1 (0.5)	1 (0.6)	3 (1.6)	3 (1.8)	1 (0.6)	1 (0.7)
Conjunctivitis	0	0	0	0	3 (1.6)	3 (1.8)	0	0
Gingivitis	0	0	1 (0.5)	1 (0.6)	2 (1.1)	2 (1.2)	2 (1.1)	2 (1.4)
Tinea infection	0	0	1 (0.5)	1 (0.6)	2 (1.1)	2 (1.2)	2 (1.1)	2 (1.4)
Candidiasis	0	0	0	0	1 (0.5)	2 (1.2)	0	0
Helicobacter infection	0	0	0	0	2 (1.1)	2 (1.2)	0	0
Pulpitis dental	0	0	0	0	1 (0.5)	1 (0.6)	2 (1.1)	2 (1.4)
Otitis media	0	0	4 (2.1)	4 (2.4)	0	0	1 (0.6)	1 (0.7)
Enterocolitis infectious	0	0	2 (1.0)	2 (1.2)	0	0	0	0
Sinobronchitis	0	0	1 (0.5)	2 (1.2)	0	0	0	0
Urethritis trichomonal	0	0	1 (0.5)	2 (1.2)	0	0	0	0
Streptococcal infection	0	0	0	0	0	0	2 (1.1)	3 (2.1)
Appendicitis	0	0	0	0	0	0	1 (0.6)	2 (1.4)

Pt-y patient-years.
[a]Medical Dictionary for Regulatory Activities version 13.0.

Retention rates in the radiographic, long-term, and self-injection studies

Retention rates over the course of the study are illustrated for each treatment group in Kaplan–Meier plots for the radiographic study in Figure 5a. Overall, retention was highest in the ETN groups; approximately 80–83% of patients remained in the study at Week 52 compared with approximately 70% in the MTX group. The difference was largely owing to the higher proportion of patients who discontinued owing to lack of efficacy in the MTX group (approximately 20%) compared with that of the ETN groups (approximately 4–8%, Figure 5a). Retention rates in the long-term and self-injection studies were comparable to those observed in the radiographic study up to Week 52 and were maintained through study completion (Figure 5b and c).

Discussion

ETN is a fully human fusion of the TNF type 2 soluble receptor and the Fc region of a type 1 human immunoglobulin G that inhibits the effect of the proinflammatory cytokine TNF-α, which plays an important role in synovitis and joint damage in RA. This comprehensive review examined the pharmacokinetics of ETN in healthy Japanese volunteers and patients with RA, as well as the efficacy and safety of ETN treatment across multiple clinical studies. The program consisted of one pharmacokinetic study in 24 healthy Japanese volunteers and six interventional clinical studies in which 821 adult Japanese patients with RA were studied for a total ETN exposure of more than 870 patient-years.

The Phase 1 pharmacokinetic study in healthy adult Japanese volunteers demonstrated that ETN is slowly absorbed (peak concentration in 47 h following a single injection) and slowly cleared from the body (elimination half-life of 80 h). Additional pharmacokinetic analyses were conducted during several of the interventional studies in Japanese patients with active RA. The serum concentration in Japanese patients with RA reached a steady-state within a month that was about twice the highest concentration achieved after a single administration; accumulation did not exceed the predicted concentration. The serum ETN concentration was
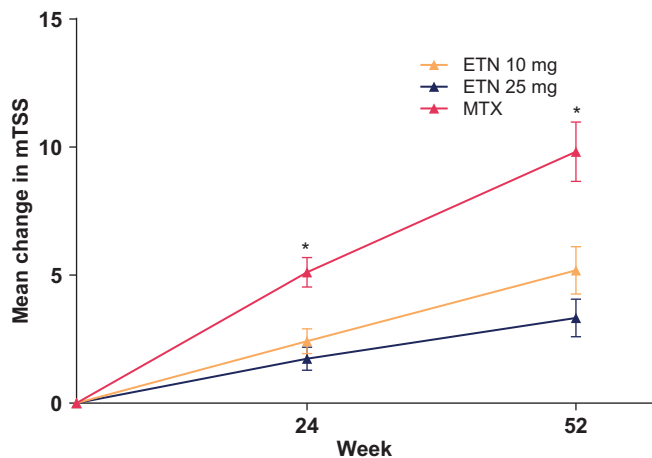
Figure 4. Mean change in modified total Sharp score (mTSS) from baseline over time in the radiographic. *$P < 0.0001$ for etanercept (ETN) 10-mg twice weekly (BIW) and ETN 25-mg BIW versus methotrexate (MTX) ≤ 8 mg/w; $P =$ not significant for ETN 10-mg BIW versus ETN 25-mg BIW and any time point. Error bars represent standard error. Adapted with permission from Takeuchi T, et al. Mod Rheumatol 23(4), 623–633, 2013 [12].

virtually constant and dose-proportional over the 52-week period, with no decreases in concentration associated with repeated dosing. Switching from BIW (ETN 25-mg BIW) to QW (ETN 50-mg QW) dosing was associated with a consistent ETN serum exposure. Therefore, the pharmacokinetic profile supports both BIW and QW dosing for ETN in the Japanese RA population.

The clinical efficacy of ETN in Japanese patients with RA has been primarily evaluated in two controlled registrational studies. While both studies included patients with active RA and who had inadequate response to conventional synthetic DMARDs, there were subtle differences in the two study populations. Some baseline disease characteristics, suggested a more advanced disease in the bridging study population; that is, longer disease duration, higher ESR, more swollen and tender joints, higher CRP, higher tender and swollen joint counts, and longer duration of morning stiffness. In the radiographic study, eligible patients were limited to a disease duration of 10 years or less, required fewer tender joint counts (≥ 6 tender joints and ≥ 6 swollen joints) and could have been either MTX naïve (36%) or could have received previous MTX treatment (64%).

In the placebo-controlled bridging study, ETN 10-mg BIW and ETN 25-mg BIW provided significant benefit in improving clinical symptoms. ACR responses and DAS28 ESR showed significant improvement as early as 2 weeks and with continued improvement up to the 12-week time point. Significant improvements over placebo also were observed in other clinical signs and symptoms, SDAI remission, CRP and ESR, as well as function (HAQ-DI). These data indicate that a robust effect size was observed for ETN when compared with placebo. Furthermore, as evidenced from the other registrational (radiographic) study, when ETN was compared with an active comparator (MTX), a clear separation from this standard oral therapy was demonstrated. Significant improvements in clinical symptoms, including ACR responses, DAS28 ESR scores and remission, and EULAR Good Response, over MTX were achieved for both ETN dose groups.

There have been no clinical studies that have directly compared ETN to other biological DMARDs. However, clinical results from the two registrational studies show that treatment with ETN monotherapy to be generally comparable to those of other approved biologics in Japanese patients with moderate to severe RA. For example, the treatment of moderate to severe RA with adalimumab monotherapy 80 mg every other week for 24 weeks

resulted in ACR50 achievement in 32% of patients [15] compared with 54% for ETN 25 mg BIW monotherapy. Treatment of moderate to severe RA with abatacept (10 mg/kg) in combination with MTX resulted in 46% of patients achieving ACR50 after 24 weeks [16]. The percentage of patients with moderate to severe RA who achieved ACR50 after 24 weeks of treatment with golimumab (100 mg every 4 weeks) in combination with MTX was 48% [17]; 42% of patients who received golimumab monotherapy achieved ACR50 [18].

In line with the clinical outcomes from the radiographic study, the radiographic outcomes data showed clear separation between the active comparator, MTX, and the 2 ETN doses in slowing the progression of joint structural damage such that after 52 weeks of treatment the change in mTSS was significantly less in ETN-treated patients. In addition, more ETN-treated patients achieved no progression of joint damage (mTSS change < 0.5; $P < 0.001$). Although the study was only 52 weeks in duration, further benefit is likely to accrue in terms of structural preservation given that the pattern of progression was linear. These results appear to be consistent with radiographic results of other biologic DMARDs, such as adalimumab, tocilizumab, and golimumab, which have been shown to reduce progression of joint structural damage in Japanese patients with RA [12,19,20].

There was evidence of a dose response for ETN 10 mg and 25 mg in terms of clinical and radiographic variables in the radiographic study. Firstly, the majority of the clinical endpoints were numerically greater in the 25-mg BIW dose group compared with those of the 10-mg BIW dose group. In addition, some clinical signs and symptoms including EULAR Good Response, physician global assessment scores, tender joint counts, radiographic nonprogression (mTSS ≤ smallest detectable difference), HAQ-DI remission (< 0.5), and Boolean remission, all showed significantly greater response to ETN 25 mg, indicating greater potential for benefit with the higher ETN dose [12]. ETN 25 mg also was consistently associated with numerically better radiographic outcomes over the 10-mg dose (i.e., ΔmTSS) throughout the 52-week study. In addition, subgroup analyses indicated that patients with factors indicating high disease activity showed better radiographic response in the higher dose group [12]. These results are consistent with an earlier study that demonstrated the radiographic superiority of ETN 25-mg BIW over ETN 10-mg BIW at 12 and 24 months in patients in North America [21]. The favorable response of the 25-mg dose observed at 52 weeks may be clinically meaningful considering that patients with RA may be treated over many years.

In the extension (long-term and the self-injection) studies, ETN continued to be effective in reducing the signs and symptoms of RA. Efficacy responses in both extension studies were shown to be either stable or tending to improve up to at least 160 weeks of therapy. Durability of response was favorable as evidenced by the high retention rates; relatively few patients dropped out of the studies.

Flexible dosing and frequency is a unique option available to Japanese rheumatologists. Two approaches were taken to evaluate the efficacy of alternative QW dosing. The first approach was based on switching patients whose disease was being controlled on ETN 25-mg BIW to ETN 50-mg QW, while the other approach involved comparing ETN 10-mg BIW with ETN 25-mg QW in a parallel group design. Clinical benefit with ETN was maintained after patients receiving 25-mg BIW were switched to a less frequent dosing regimen of ETN 50-mg QW for 8 weeks. In the 10-mg BIW versus 25-mg QW study, clinical efficacy (improvement in DAS28 ESR scores [primary efficacy measure] and ACR responses) of both dosing regimens was shown to be similar. There were no significant differences between the ETN treatment regimens in DAS28 ESR scores at any time point. The two alternative
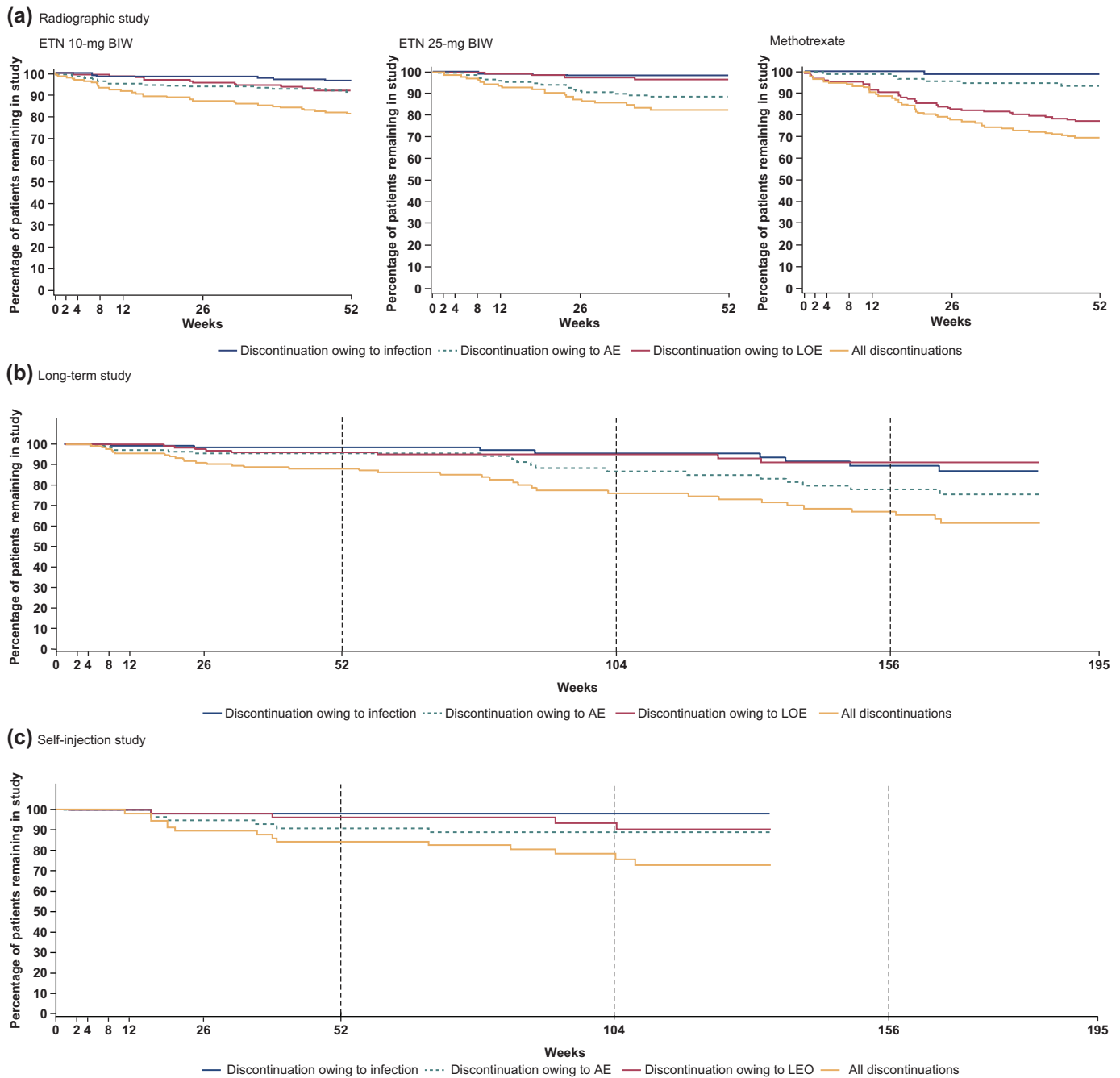
(a) Radiographic study

Figure 5. Time to discontinuation during the radiographic and extension studies. (a) Radiographic study (52 weeks). (b) Long-term study (182 weeks). (c) Self-injection study (132 weeks). *ETN* etanercept; *BIW* twice weekly; *AE* adverse event; *LOE* loss of efficacy.

dosing studies support the flexibility of offering options of QW or BIW dosing in Japanese patients with RA.

ETN was generally well tolerated in these studies of Japanese patients with RA. No new or unexpected safety signals were detected when compared with previous reports on ETN in non-Japanese patients with RA. There were no medically relevant safety differences noted between the two ETN doses or between the QW or BIW dosing regimens. The tolerability of ETN monotherapy in these studies was comparable to post-marketing surveillance analyses that showed overall rates of adverse events of 31–35% [8,10]. Post-marketing surveillance studies have shown that adalimumab [22] has a similar rate of adverse events (31%). Post-marketing surveillance studies also have found that patients with short disease duration (< 2 years) have lower incidence of adverse events than patients with longer disease durations (> 5 years) [9]. As expected, the cumulative rate of serious infections

was higher in the pooled bridging and long-term extension studies (14%) than in the 52-week radiographic study (MTX 0.6%; ETN 10 mg BIW 1.0%; ETN 25 mg BIW 0%). These data are comparable to previous studies that show that the risk incidence of serious infections increases with longer exposure periods in patients treated with ETN and infliximab [23,24].

Pulmonary bacterial infections, tuberculosis, and opportunistic infections are of special concern in Japanese patients with RA [24–27]. PCP is regarded as an important treatment-related infection because it accounts for the majority of acute-onset diffuse interstitial lung disease in RA patients treated with biologics [28]. Treatment with biological DMARDs has been shown to be associated with elevated occurrence of interstitial pulmonary diseases, including PCP [22,29], and guidelines for the administration of ETN clearly recommend that patients with a history of PCP be excluded from treatment with any TNF inhibitor [5,6]. Recent

evidence suggests that the association between TNF inhibitory treatments and interstitial pulmonary diseases is less certain and instead, RA is more closely associated with pulmonary infections than biologic treatments [30]. While the patients in these studies did not experience opportunistic infections (such as PCP, hepatitis B, or hepatitis C) or tuberculosis, these conditions have been seen in post-marketing surveillance studies for infliximab (bacterial pneumonia 2.2%; tuberculosis 0.3%; PCP 0.4%; interstitial pneumonitis 0.5%) [27] and adalimumab (bacterial pneumonia 1.2%; interstitial pneumonia 0.6%; PCP 0.3%; tuberculosis 0.1%) [22], and post-marketing surveillance of ETN showed incidence of pneumonia (0.8%), tuberculosis (0.1%), and interstitial lung disease (0.6%) [7].

Overall, the occurrence of malignancies in these studies was limited to 4 cases: 2 cases of breast cancer, 1 hypopharyngeal cancer, and 1 liposarcoma. Based on the exposure of 870 patient-years, the exposure-adjusted event rate in Japanese patients with RA was 0.460 events per 100 patient-years. In an analysis of the larger global trial population in European, North American, and Japanese patients treated with ETN including 18,263 patient-years of exposure from a total of 49 clinical trials, the standardized incidence ratio (95% confidence interval) for malignancies was 1.00 (0.83–1.19). These results indicate that the risk of malignancy in ETN-treated patients is not elevated compared with the risk in the general population (SEER database) [31].

The patient retention rate of ETN was reported to be longer in comparison with other biologics including infliximab, and adalimumab [32,33]. One of the primary reasons for discontinuation among patients treated with adalimumab was lack of efficacy [22,33]. In the radiographic study, the rate of discontinuations due to lack of efficacy in ETN-treated patients was low relative to that for MTX-treated patients; the major cause of discontinuation was owing to adverse events. The primary reason for discontinuation in the long-term and self-injections studies also was due to adverse events; relatively few patients discontinued ETN due to lack of efficacy. These data are consistent with previous findings [8,10].

A systematic review and meta-analysis showed that immunogenicity of anti-TNF therapy with adalimumab or infliximab in immune-mediated inflammatory diseases reduces therapeutic response as much as 80%, while antibodies to ETN were not detected [34]. Consistent with that study, the immunogenicity of ETN in Japanese patients with RA was of limited clinical importance in the bridging, long-term, and self-injection studies. The antibodies that were detected in these studies were generally transient in nature and varied from 2 to 10% at any given time point, with no impact on drug response. These data suggest the presence of "binding antibodies" or false positive results since the enzyme-linked immunosorbent assays used were of low specificity. Also consistent with previous reports of immunogenicity in non-Japanese patients, no neutralizing anti-drug antibodies have been identified in these studies featuring Japanese patients with RA.

The extensive ETN clinical program has provided results supporting clinical efficacy, inhibition of radiographic progression, and safety that are consistent with a well-defined, favorable, and predictable risk benefit for patients with RA in Japan. Conventional synthetic DMARDs, including MTX, are widely used for treatment of RA, but may not be tolerated by all patients; clinical trial data for ETN monotherapy is internationally limited [34,35]. In a recent analysis of post-marketing study data from 1334 medical sites in Japan, 26.1% of patients (3616/13,861) were treated with ETN monotherapy [36]. Thus, clinical evaluation of ETN monotherapy is important. Flexible dosing and frequency of ETN is indicated in Japan, providing a unique opportunity for rheumatologists to tailor treatment for each patient. Administration of ETN in various doses

and frequencies is shown herein to be an effective treatment option for Japanese patients with RA.

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Supplementary material available online

Supplementary Figures 1–6 and Tables 1–7.