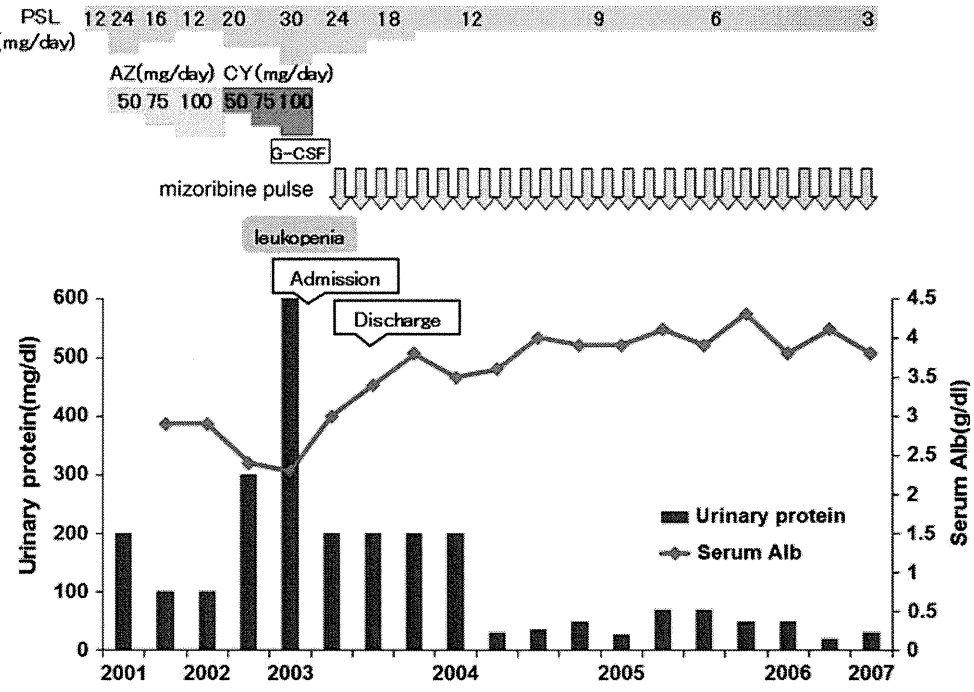

Fig. 2 Clinical course of a representative case (case 1)

treatment in the management of collagen vascular diseases. This mizoribine pulse therapy seems to be effective, and should be attempted instead of the approved mizoribine therapy for refractory lupus nephritis. A prospective comparative study between mizoribine pulse therapy and the standard approved therapy should also be performed to confirm the efficacy of this therapeutic strategy.

Conflict of interest None.

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ORIGINAL ARTICLE

No increased mortality in patients with rheumatoid arthritis treated with biologics: results from the biologics register of six rheumatology institutes in Japan

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Abstract
Objective To investigate the influence of biologics on mortality and risk factors for death in rheumatoid arthritis (RA) patients.
Methods RA patients treated with at least one dose of biologics in daily practice in six large rheumatology institutes ("biologics cohort") were observed until 15 May 2010 or death, whichever occurred first. Mortality of the biologics cohort and the "comparator cohort" (comprising patients among the IORRA cohort who had never been treated with biologics) was compared to that of the Japanese general population. Factors associated with mortality were assessed by a Cox model.
Results Among 2683 patients with 6913.0 patient-years of observation, 38 deaths were identified in the biologics cohort. The probability of death in patients lost to follow-up, calculated using the weighted standardized mortality ratio (SMR), was 1.08 [95 % confidence interval (CI) 0.77–1.47] in the biologics cohort and 1.28 (95 % CI 1.17–1.41) in the comparator cohort. Pulmonary involvement was the main cause of death (47.4 %), and the disease-specific SMR of pneumonia was 4.19 (95 % CI 1.81–8.25). Risk factors for death included male gender [hazard ratio (HR) 2.78 (95 % CI 1.24–6.22)], advanced age (HR 1.07, 95 % CI 1.03–1.11), and corticosteroid dose (HR 1.08, 95 % CI 1.01–1.17).
Conclusion Mortality in RA patients exposed to biologics did not exceed that in patients not exposed to biologics, but death from pulmonary manifestations was proportionally increased in RA patients exposed to biologics.

Keywords Biologics · Cause of death · Mortality · Rheumatoid arthritis · Standardized mortality ratio

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that results in worsening physical function and extra-articular manifestations. Due to these manifestations, patients with RA have been reported to experience excessive mortality in Western countries [1–6]. Comparably worse mortality has recently been reported for Japanese patients with RA [7]. However, the cause of death differs

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greatly between Western and Japanese RA patients [7]. The main cause of death in Western RA patients is cardiovascular disease (CVD), comprising 40–50 % of deaths. In contrast, one-quarter of Japanese RA patients die from malignancy and respiratory disease, respectively, with pneumonia and interstitial lung disease being the two equivalent primary causes of respiratory disease [7].

Many studies have reported favorable results of biologic treatment of RA in decreasing disease activity, preventing bone destruction, and suppressing CVD events and death [8–11], and possibly improving overall mortality [8, 12, 13] in Western RA patients. However, several reports have demonstrated that use of anti-tumor necrosis factor (TNF) therapy is associated with an increased risk of serious infection, especially in the first six months of treatment [14, 15]. Considering that previous reports [7, 16–18] indicate that the causes of death of Japanese RA patients differ from those of Western RA patients, it is yet to be clarified whether biologic treatment results in the same benefit to Japanese RA patients as that reported for Western RA patients.

We conducted this study to elucidate whether treatment of RA with biologics actually provides an improvement in the mortality of Japanese RA patients and to assess causes of death and risk factors for death in a multicenter observational cohort study.

Patients and methods

Study design

All of the patients with RA who had been treated with at least one dose of a biologic (including infliximab, etanercept, tocilizumab and adalimumab) in daily clinical practice were listed in six rheumatology centers, and these patients were registered into the "biologics cohort" at the start of this observational study in September 2008. Additional new RA patients who were treated with at least one dose of these biologics after September 2008 were introduced into this biologics cohort and both were observed until 15 May 2010 or until death, whichever came first. A query about their survival was sent to the patients who were lost to follow-up at the end of this observational period by the relevant physician. This study was conducted through the cooperation of six large rheumatology centers in Japan: the Institute of Rheumatology of Tokyo Women's Medical University, the Department of Rheumatology and Clinical Immunology of Saitama Medical Center in Saitama Medical University, the First Department of Internal Medicine of the University of Occupational and Environmental Health, Japan, the Department of Orthopedic Surgery and Rheumatology of Nagoya University, the Department of Diabetes, Endocrinology and Rheumatology of Japanese Red Cross Kyoto Daiichi Hospital, and the Division of Rheumatology and Clinical Immunology of Jichi Medical University. This study was conducted after approval was given by the ethical committee at each institute. The use of biologics in daily practice was judged by responsible rheumatologists, with reference to the guideline for the introduction of biologics in practice developed by the Japanese College of Rheumatology.

Assessments

The baseline data of the patients who had received a biologic agent (infliximab, etanercept, tocilizumab, or adalimumab) were collected, including age, sex, disease duration, concomitant methotrexate (MTX) use and dose, concomitant corticosteroid use and dose (converted into the equivalent prednisolone dose) at the initiation of the corresponding biologic, and when and which biologic agent was introduced. Medical history, including tuberculosis, malignancy, CVD, cerebrovascular disease, and gastrointestinal bleeding was reported. Disease activity was assessed by either DAS28 or DAS28-CRP [19] according to their utilization at each institute. Physical function was also measured either by Health Assessment Questionnaire (HAQ), the Japanese version of the HAQ (J-HAQ) [20], or the modified HAQ (M-HAQ). When the biologic agent was discontinued, the time and reason for discontinuation were reported. In cases where the patient had switched biologics, the biologics used during the observational period were recorded. Patients who received at least one dose of a biologic were followed up even if they discontinued the agent or switched to an alternative biologic agent. At the end of this study, on 15 May 2010, the survival of each patient was confirmed as accurately as possible, as described below. Causes of death were collected from each institute and classified according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10).

The primary outcome measure in this study was mortality. The notification of death and the cause of death were acquired from the relevant physician at each rheumatology institute. When the patient's survival was uncertain at the end of this study period, a letter to confirm their survival was sent by the affiliated institute. When the death of the patient was approved, cause of death and time were reported.

Comparison cohorts

Patients with RA who were enrolled in the IORRA (Institute of Rheumatology, Rheumatoid Arthritis) cohort after April 2003 (around which time the first biologic agent

became available in daily practice in Japan) and who had never been treated with any biologics until 15 May 2010 were included in the "comparison cohort" (nonbiologics IORRA) in this study. IORRA is a large observational cohort established in 2000 at the Institute of Rheumatology, Tokyo Women's Medical University, with the primary aim being to assess standard RA outcomes in accordance with the current treatments used in daily practice, as reported precisely previously [7, 21, 22]. The IORRA cohort basically comprises all RA patients who attended the Institute of Rheumatology, Tokyo Women's Medical University, and fulfilled the classification criteria of the American College of Rheumatology for RA [23] in principle after informed consent was obtained. The IORRA survey is conducted biannually (in April and May and in October and November). Disease activity evaluated by DAS28 [19], physical function evaluated by J-HAQ [20], and laboratory data used in daily practice were collected. Medications, including disease-modifying antirheumatic drugs (DMARDs), MTX, corticosteroids, and biologics used within the previous six months were also reported. Active follow-up by mail was conducted for patients who did not attend the subsequent IORRA survey. The cause and the time of the death were collected from the physicians at the affiliated hospitals, from residual family members through active follow-up inquiry by mail, and from the police when it was sudden or accidental.

Statistical analysis

Mortality

The mortality of patients in this biologics cohort was compared to the mortality of the Japanese general population reported by Japanese Health and Wealth (http://www.stat.go.jp/data/nihon/02.htm) via standardized mortality ratios (SMRs) and confidence intervals (95 % CIs). Standardization was conducted by the calendar year of recruitment, gender, and age. Since this biologics cohort study was observational, patients were not completely followed unless an active effort was made to capture their survival status. Nonresponse to mailed queries is a potential source of bias in this type of research survey. Thus, to assess mortality, we attempted to statistically analyze it as follows. First, we assumed that all patients who were lost to follow-up at the end of the observation period were alive; the SMR was then calculated and compared to the Japanese general population (analysis 1). Second, we assumed that patients who were ascertained to be alive at three months (analysis 2) or six months (analysis 3) before the end of the observation period were alive at the end of the observational period; these data were compared to those of the Japanese general population. Finally, as Kauppi et al. [24] reported that patients with RA who did not respond to mailed queries were 1.65 times more likely to have died over the two-year follow-up period compared to responders, we statistically determined that patients who were lost to follow-up would have died at this rate (analysis 4), and these data were compared to those of the Japanese population.

The mortality of the patients in the comparison cohort (non-biologics IORRA) was analyzed using SMR with the same weighting as in analysis 4, assuming the patients who were lost to follow-up were 1.65 times more likely to have died over the two-year follow-up period than the Japanese general population (analysis 5).

Causes of death and disease-specific mortality

The causes of death in this biologics cohort were collected and cause-specific mortality was analyzed for malignancy, pneumonia, and respiratory diseases including pneumonia. Death within three months of the last use of biologics was considered "death on biologics." For patients who were ascertained to have died due to a specific cause of death, the disease-specific mortality rate and SMR were calculated by comparing to the mortality of the Japanese general population reported by Japanese Health and Wealth (http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/suii01/deth10.html).

Risk factors for mortality

To assess the risk factors for mortality among patients who had been exposed to at least one dose of a biologic, variables including sex, age (year), body mass index (BMI) (kg/m^2), disease duration (year), disease activity (DAS28), MTX dose (mg/week), and corticosteroid dose (mg/day) at the initiation of the first biologics were analyzed using a Cox model.

Results

Overall, 2683 patients with RA who had been exposed to biologics were registered into the biologics cohort. The first biologics used in these patients included infliximab (n = 1112, 41.2 %), etanercept (n = 1053, 39.0 %), adalimumab (n = 345, 12.8 %), tocilizumab (n = 173, 6.4 %), and abatacept (n = 4, 0.1 %). The mean (SD) age was 56.0 (13.9) years, mean disease duration was 10.1 (10.1) years, and 84.0 % of patients were women (Table 1). Baseline disease activity was 5.6 (1.2) as evaluated by DAS28 or 4.9 (1.2) by DAS28-CRP. MTX and corticosteroids were concomitantly prescribed in 77.7 and 54.2 % of patients, respectively. Discontinuation of the

Table 1 Baseline characteristics of the biologics cohort

	Percentage or mean	SD
Female (%)	84.0	
Age (years)	56.0	13.9
Disease duration (years)	10.1	10.1
BMI (kg/m^2)	21.5	3.4
General VAS	57.0	23.5
Disease activity		
DAS28	5.6	1.2
DAS28-CRP	4.9	1.2
ESR (mm/h)	54.9	30.2
CRP (mg/dl)	3.10	3.40
RF (IU/ml)	202.4	348.2
Physical dysfunction (HAQ, J-HAQ, MHAQ)	1.17	0.81
EQ-5D	0.62	0.13
Past history		
Pulmonary tuberculosis (%)	3.4	
Malignancies (%)	4.5	
Ischemic heart diseases (%)	1.4	
Cerebrovascular disease (%)	1.3	
GI bleeding (%)	1.0	
MTX use (%)	77.7	
MTX dose (mg/week)	7.6	3.2
Corticosteroid use (%)	54.2	
Prednisolone dose (mg/day)	3.9	3.4

Data shown are the % or mean (standard deviation) values, as appropriate

VAS visual analogue scale, *DAS28* disease activity score 28, *ESR* erythrocyte sedimentation rate, *CRP* C reactive protein, *RF* rheumatoid factor, *HAQ* health assessment questionnaire, *EQ-5D* EuroQoL 5 dimension, *GI* gastrointestinal, *MTX* methotrexate

first biologic was reported in 36.1 % of patients. Reasons for discontinuation of biologics included great response (7.1 %), insufficient effect (38.6 %), side effects (19.8 %), and economic reasons (2.9 %). Among patients who discontinued their first biologic, 43.2 % of patients switched to a second biologic. During this observation period, 64.8 % of patients were treated with one biologic, 17.2 % were treated with two biologics, and 18.0 % were treated with three or more biologics.

Mortality

Thirty-eight deaths were recorded among 6913.0 patient-years (1072.4 patient-years for males and 5840.6 patient-years for females) of observation in the biologics cohort, and 537 patients (20.0 %) were lost to follow-up. SMRs were calculated with several assumptions (Table 2). When assuming that all of the patients lost to follow-up were alive, the SMR of RA patients treated with biologics did not exceed that of the Japanese general population [analysis 1, SMR 1.02 (95 % CI 0.72–1.40)]. When assuming that the patients who were ascertained to be alive at three months (analysis 2) or six months (analysis 3) before the end of the observation period were alive, the assumed SMR for the general population was 2.17 (95 % CI 1.73–2.70) in analysis 2 and 1.96 (95 % CI 1.54–2.46) in analysis 3. Upon weighting for patients lost to follow-up at the end of the observation period using the 1.65 times death assumption (as described in "Patients and methods"), the SMR in this biologics cohort (analysis 4) was 1.08 (95 % CI 0.77–1.47) compared with that of the Japanese general population [1.45 (95 % CI 0.86–2.30) in males and 0.90 (95 % CI 0.57–1.35) in females].

When the same weighting for patients lost to follow-up was applied to the nonbiologics IORRA cohort, the assumed SMR was 1.28 (95 % CI 1.17–1.41) for all subjects [1.31 (95 % CI 1.11–1.53) for males and 1.27 (95 % CI 1.13–1.43) for females] as compared to the Japanese general population.

Causes of death and cause-specific mortality

The most frequent cause of death was respiratory disease (47.4 %), including pneumonia (21.1 %) and interstitial lung disease (18.4 %), followed by infection other than pneumonia and malignancies (Table 3). When only deaths that occurred within three months of the last administration of biologics were considered, deaths from respiratory disease (58.8 %) including pneumonia (23.5 %) and interstitial pneumonia (23.5 %) were most prominent.

Concerning disease-specific mortality, deaths from malignancy in RA patients treated with biologics did not exceed those in the Japanese general population [malignancy-specific SMR, 0.30 (95 % CI 0.10–0.69)]; however, deaths from pneumonia (pneumonia-specific SMR 4.19, 95 % CI 1.81–8.25) and respiratory disease (respiratory-specific SMR 9.42, 95 % CI 5.58–14.88) were much higher than those in the Japanese general population (Table 4).

Risk factors for mortality

Risk factors for mortality (analyzed by a Cox proportional hazards model) were male gender [hazard ratio (HR) 2.78 (95 % CI 1.24–6.22), $p < 0.05$], older age [HR 1.07 (95 % CI 1.03–1.11), $p < 0.001$], and corticosteroid dose [HR 1.08 (95 % CI 1.01–1.17), $p < 0.05$], as shown in Table 5.

Discussion

This is the first study to deal with mortality in patients with RA treated with biologics in Japan. In general, the

Table 2 Adjusted mortality rates and standardized mortality ratios (SMRs) of biologics-treated rheumatoid arthritis patients ("biologics cohort") and rheumatoid arthritis patients among the IORRA cohort who had never taken biologics ("nonbiologics IORRA cohort") as compared to the Japanese general population

	Observed	Observation (patient-years)	Crude rate/100,000 patient-years	Adjusted mortality rate			SMR		
				Per 100,000 patient-years	95 % lower	95 % upper	SMR	95 % lower	95 % upper
Analysis 1: biologics cohort (assuming that all patients who were lost to follow-up at the end of observation period are alive)									
Total	38	6913.03	834.29	423.60	228.50	717.67	1.02	0.72	1.40
Male	17	1072.41	921.50	672.03	301.05	1292.97	1.40	0.81	2.24
Female	21	5840.62	751.05	186.49	93.43	332.87	0.84	0.52	1.28
Analysis 2: biologics cohort (assuming that all patients who were ascertained to be alive at three months before the end of the observation period were alive)									
Total	81	6913.03	834.29	700.08	470.12	1003.22	2.17	1.73	2.70
Male	23	1072.41	921.50	846.01	434.85	1483.29	1.89	1.20	2.84
Female	58	5840.62	751.05	560.79	393.21	775.65	2.31	1.76	2.99
Analysis 3: biologics cohort (assuming that all patients who were ascertained to be alive at six months before the end of the observation period were alive)									
Total	73	6913.03	834.29	628.58	406.84	927.81	1.96	1.54	2.46
Male	22	1072.41	921.50	821.43	414.13	1459.73	1.81	1.13	2.74
Female	51	5840.62	751.05	444.52	307.90	621.07	2.03	1.51	2.67
Analysis 4: biologics cohort (assuming that patients who were lost to follow-up were 1.65 times more prone to die)									
Total	40.20	6913.03	834.29	442.73	243.45	739.70	1.08	0.77	1.47
Male	17.65	1072.41	921.50	691.31	314.95	1315.47	1.45	0.86	2.30
Female	22.55	5840.62	751.05	205.47	102.56	367.66	0.90	0.57	1.35
Analysis 5: nonbiologics IORRA cohort (assuming that patient who were lost to follow-up was 1.65 times more prone to die)									
Total	445.86	39078.17	1140.94	743.37	628.64	872.98	1.28	1.17	1.41
Male	161.19	6775.95	2378.91	814.48	648.09	1010.55	1.31	1.11	1.53
Female	284.66	32302.21	881.25	675.50	522.91	858.72	1.27	1.13	1.43

investigation of mortality is conducted by accessing death certificates or death records provided by the government or local government. However, there is no national death database in Japan, and it is quite difficult to access death certificates, even from local governments. Thus, we attempted to register as many cases as possible from the institutes that participated in this study, and to monitor death information actively in each clinical environment. IORRA was used as an external control population, since the IORRA cohort is considered to be representative of Japanese RA patients in a real-world setting and is the only cohort in which mortality of RA patients has been analyzed and published [7]. In this study, we demonstrated that the mortality of Japanese RA patients treated with at least one dose of biologics in daily practice did not exceed that in the Japanese general population, whereas the mortality of patients among the IORRA cohort who had never been treated with biologics slightly exceeded that seen in the Japanese general population. Even though these two cohorts came from different populations, it is hoped that treatment with biologics may improve the mortality of patients who can be treated with biologics. This result is comparable to recent reports from Western countries [12, 13, 25]. In those countries, information on comorbidity, hospitalization, and death can be obtained from nationwide registries, making it possible to calculate mortality more accurately, even though patients lost to follow-up are not mentioned. In this study, the number of patients who were lost to follow-up was relatively large, so the sensitivity analysis need to be executed by using assumption according to the report of Kauppi et al. How best to manage patients who are lost to follow-up (which inevitably occurs in this type of study) is a major issue to be solved.

The result that patients who were treated with at least one dose of biologics have a better outcome needs to be interpreted carefully, because we compared SMRs from different sources. The potential for selection bias in this study should be considered. First of all, patients who were candidates for biologics treatment were expected to tolerate the biological therapy. Second, patients who receive biologics were carefully screened for occult infections, malignancies, and comorbidities such as respiratory diseases before treatment. Thirdly, they were also monitored more extensively during the treatment, so adverse events, including upper respiratory infections and malignancies,

were more likely to have been identified in the biologic cohort beforehand. However, this possible selection bias favoring less severe complications in the biologic cohort does not completely explain our results. Additional considerations include the fact that 25.9 % of patients discontinued biologics during the observation period, and the average 2.6 years of the observation performed in this study may not have been long enough to sufficiently evaluate mortality.

Respiratory diseases, primarily pneumonia and interstitial lung disease, were the predominant causes of death in this biologics cohort, followed by infections other than pneumonia, malignancy, and CVD. In Western countries, CVD is the major cause of death in the general population, and it affects a larger proportion of patients with RA. Biologics, mainly anti-TNF agents, are expected to reduce the incidence and risk of cardiovascular events and improve mortality [11, 26], but CVD is still the main cause of death in Western RA patients treated with biologics. In contrast, rates of respiratory diseases (especially pneumonia) in this biologics cohort were significantly high, and the disease-specific SMR for pneumonia was about four times higher than that of the Japanese general population. When we considered deaths limited to within three months of the last use of biologics, 58 % of these particular RA patients died from respiratory diseases, including pneumonia; in other words, pneumonia and respiratory diseases tended to occur while using biologics. Interstitial lung disease is one of the major causes of death in Japanese patients with RA, accounting for half of all cases of respiratory disease; this was also true in this biologics cohort. Recently, interstitial lung disease has been extensively discussed in the context

Table 3 Causes of death classified according to ICD-10 chapter number in patients with rheumatoid arthritis treated with biologics

Chapter	Blocks	Chapter title	Total deaths ($N = 38$), n (%)	Death within three months after the last use of biologics ($N = 17$), n (%)
I	A00–B99	Certain infections and parasitic diseases	6 (15.8)	2 (11.8)
II	C00–D48	Malignancies	5 (13.2)	2 (11.8)
IV	E00–E90	Endocrine, nutritional and metabolic diseases	1 (2.6)	
IX	I00–I99	Diseases of the circulatory system	5 (13.2)	1 (5.9)
	I20–I25	Ischemic heart diseases	2 (5.3)	1 (5.9)
	I60–I69	Cerebrovascular diseases	2 (5.3)	
X	J00–J99	Diseases of the respiratory system	18 (47.4)	10 (58.8)
	J10–J18	Influenza and pneumonia	8 (21.1)	4 (23.5)
	J99	Rheumatoid lung disease	7 (18.4)	4 (23.5)
XVIII	R00–R99	Symptoms, signs and abnormal clinical and laboratory findings not classified elsewhere	3 (7.9)	2 (11.8)

ICD-10 International Statistical Classification of Disease and Related Health Problems, Tenth Revision

Table 4 Disease-specific mortalities and standardized mortality ratios (SMRs) of patients treated with at least one dose of biologics

Observed	Patient-years	Adjusted mortality rate	Per 100,000 patient-years	95 % CI	SMR	95 % CI
Malignancies						
Total	5	6913.03	44.92	10.90–121.78	0.30	0.10–0.69
Male	2	1072.41	65.79	7.94–237.93	0.37	0.04–1.33
Female	3	5840.62	24.93	5.09–73.15	0.26	0.05–0.76
Pneumonia						
Total	8	6913.03	189.42	62.16–439.46	4.19	1.81–8.25
Male	5	1072.41	317.29	82.41–832.08	6.82	2.21–15.91
Female	3	5840.62	66.96	5.81–270.49	2.55	0.52–7.44
Respiratory diseases						
Total	18	6913.03	309.65	151.55–561.60	9.42	5.58–14.88
Male	9	1072.41	455.74	177.50–957.40	12.27	5.61–23.29
Female	9	5840.62	169.72	51.81–409.58	7.64	3.49–14.51

SMR standardized mortality ratio, *95 % CI* 95 % confidence intervals

Table 5 The risk factors for death in patients with rheumatoid arthritis treated with at least one dose of biologics

	Coefficient	HR	95 % CI	*p*
Male sex	1.021	2.78	1.24–6.22	0.013
Age (years)	0.068	1.07	1.03–1.11	<0.001
Disease duration (year)	−0.024	0.98	0.93–1.02	0.291
DAS28	−0.133	0.88	0.64–1.20	0.404
Methotrexate dose (mg/week)	−0.042	0.96	0.87–1.06	0.389
Steroid dose (mg/day)	0.081	1.08	1.01–1.17	0.029

HR hazard ratio, *95 % CI* 95 % confidence interval, *DAS28* 28-joints disease activity score

of treatment with or without biologics [6, 27, 28]; thus, reducing the incidence and mortality of interstitial lung disease in this patient population is an important issue.

We have demonstrated that risks for mortality included age, male gender, and corticosteroid dose at the initiation of the first biologic in this biologics cohort. Jacobsson reported that disability, VAS for pain, and presence of comorbidity (COPD, diabetes, or CVD) were strong predictors of mortality according to time-dependent proportional hazards models. In this study, we could not perform time-dependent analysis because it was difficult to obtain all of the required data on physical function and VAS for pain. In addition, as we did not establish any central adjudicative committee for this study, each institution needed to authorize the recording of data on comorbidity and death. Thus, it was difficult to obtain that information in this study. However, we found that the dose of corticosteroids at the initiation of the first biologic was a risk factor for mortality. It is the consensus that the concomitant use of corticosteroids is a risk factor for mortality in patients with RA, even though corticosteroids are more likely to be prescribed to patients in whom immunosuppressants—including biologics—are not indicated due to comorbidities.

In conclusion, this study demonstrated that no increase in mortality was associated with the introduction of biologics during RA treatment in Japan. This important issue should be further studied through an improved methodology for assessing mortality, including access to death certificates.

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A merged presentation of clinical and radiographic data using probability plots in a clinical trial, the JESMR study

In terms of the relationship between synovial inflammation and radiographic changes, including both joint damage repair and progression,[1] in rheumatoid arthritis (RA), pre-existing joint damage and persistent synovitis may promote joint destruction, while in the absence of synovitis, damaged joints may heal.[2 3] Although presentation of radiographic results using cumulative probability plots has substantially improved understanding of clinical trial data,[4] the effects of treatments on radiographic progression and improvement (regression) in individual RA patients has not yet been fully explained.

In the JESMR study,[5 6] 151 active RA patients unresponsive to treatment with methotrexate (MTX) were randomised into 1 of 2 treatment groups: etanercept (ETN) 50 mg/week with 6–8 mg/week of MTX (the E+M group), or ETN alone (the E group). Radiographs of the hands and feet before ETN (baseline) and during the first year of treatment were available from 53 (72%) and 68 (88%) patients in the E and E+M groups, respectively. Baseline characteristics of patients were comparable between those with and without available radiographic data in each treatment group (data not shown). However, most patients without data did not complete the study up to Week 52 as per protocol, chiefly due to lack of efficacy in the E group.[6] The mean baseline total Sharp-van der Heijde score (TSS)[7] was 114.5 in the E group and 113.1 in the E+M group (disease duration: 10.0 years and 8.4 years, respectively), and the smallest detectable change (SDC) in TSS over 52 weeks was 1.9.

Cumulative probability plots provided by the American College of Rheumatology (ACR)-N[8] clearly demonstrated a superior response (figure 1A,B) and a significantly greater ACR50 response rate in the E+M group at week 52 (76.5% vs 50.9%, p=0.0041, Fisher's exact test). Merged probability plots of individual radiographic change over 52 weeks (ΔTSS) suggested preferential existence of aggressive radiographic progressors among ACR50 non-responders in the E group. The relationship among treatment, clinical disease activity, and radiographic change was further addressed using time-averaged disease activity score of 28 joints (DAS28) over 52 weeks in place of ACR-N at Week 52 (figure 1C,D). Significant correlation between time-averaged DAS28 and ΔTSS was observed in the E (r^2=0.097, p=0.023) but not the E+M group (r^2=0.019, p=0.26). Aggressive radiographic progression was preferentially observed among patients with moderate or high activity on average in the E group (figure 1C), while in the E+M group, radiographic progression among these patients seemed to be balanced by radiographic regression among those in remission or with low disease activity (figures 1D–F).

The absence of radiographic regressors (>SDC) among clinical responders in the E group (figure 1A,C,E) was surprising, although 18.2% of those patients showed regression within the SDC. This may be partly explained by the limitations of the study due to the small number of patients involved. Another limitation was much lower MTX dose at study enrolment than the current global standard dosage: 7.0±1.4 (the mean±SD) and 7.4±1.1 in the E and E+M groups, respectively.

In summary, we first demonstrated the relationship between individual clinical responses and radiographic changes by merging cumulative probability plots of ACR-N or time-averaged DAS28 and ΔTSS. These presentations clearly show the relationships between two parameters as a whole, facilitating further post hoc analyses of clinical trials. Further, merged presentation of probability plots is useful in comparing a single parameter (eg, health assessment questionnaire-disability index: HAQ-DI) before and after treatments (figure 2). However, merged presentation of probability plots must be followed by statistical analyses after being classified into binary or ternary categories, as we showed here.

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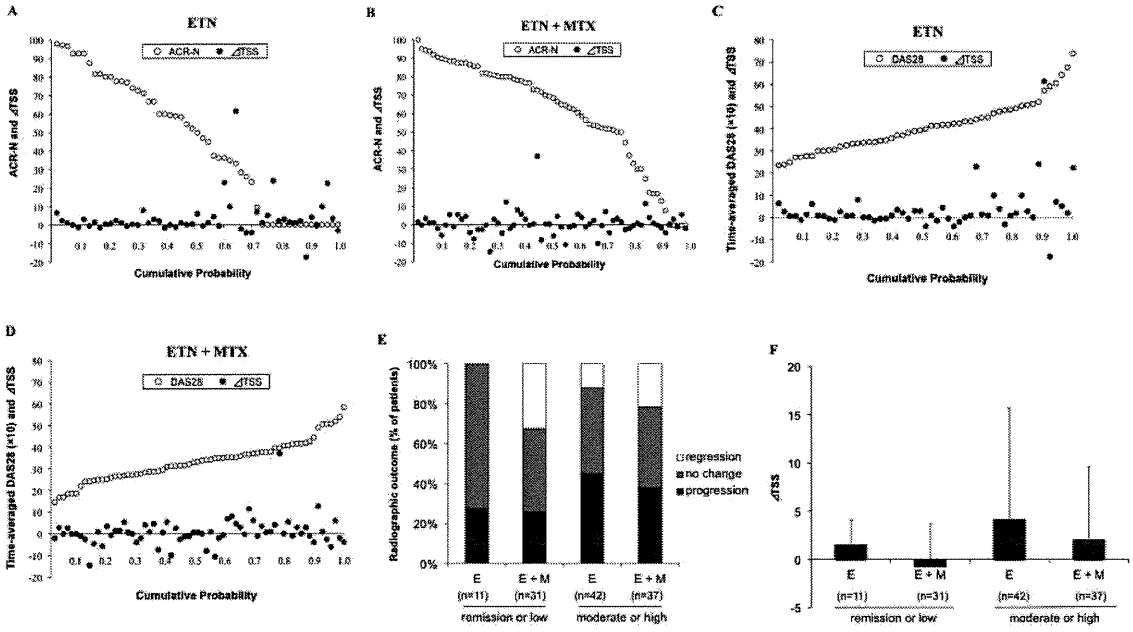

Figure 1 Cumulative probability plot analysis of ACR-N (A,B) or time-averaged DAS28 (C,D) and radiographic changes in the E (A,C) and E+M groups (B,D), merged to keep same patients on the vertical line, followed by the radiographic outcomes (E) and changes (F) stratified by the treatment and time-averaged disease activity state. Time-averaged DAS28 was calculated by the area under the curve of DAS28 at weeks 0, 2, 4, 8, 12, 24 and 52, divided by 52. No significant differences were observed between groups using Pearson's test (E) and Kruskal-Wallis test (F). ACR, American College of Rheumatology; DAS28, disease activity score of 28 joints; ETN, etanercept; MTX, methotrexate; TSS, total Sharp-van der Heijde score.

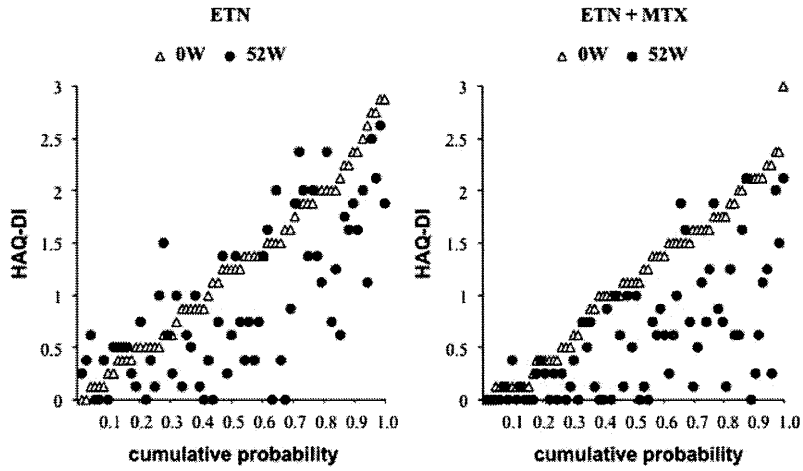

Figure 2 Merged probability plots of individual health assessment questionnaire-disability index (HAQ-DI) scores at baseline (open triangle) and Week 52 (closed circle) in the E (left) and E+M groups (right). Subsequent analyses included comparison of the rate of HAQ-DI≤0.5 at 52 weeks in patients with baseline HAQ-DI>1.5. None of 15 patients (0.0%) in the E group and 6 of 23 patients (26.1%) in the E+M group, respectively; p=0.037 by Fisher's exact test (one-sided). ETN, etanercept; MTX, methotrexate.

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AP&T Alimentary Pharmacology and Therapeutics

Randomised clinical trial: esomeprazole for the prevention of nonsteroidal anti-inflammatory drug-related peptic ulcers in Japanese patients

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SUMMARY

Background
The use of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug (NSAID)-induced gastrointestinal adverse events is well documented. However, data regarding the efficacy and safety of this approach in Japan are scarce.

Aim
To evaluate the efficacy and tolerability of esomeprazole in preventing NSAID-induced peptic ulcers in Japanese at-risk patients.

Methods
Male and female Japanese adult patients (aged $\geq$20 years) with endoscopically confirmed history of peptic ulcers who required long-term oral NSAID therapy for a chronic inflammatory condition were randomised to 24 weeks' treatment with esomeprazole 20 mg once daily or matching placebo. The primary end point was the Kaplan–Meier estimated proportion of ulcer-free patients.

Results
Overall, 343 patients were randomised to treatment (esomeprazole, $n = 175$; placebo, $n = 168$). The Kaplan–Meier estimated ulcer-free rate over the 24-week treatment period was significantly higher (log-rank $P < 0.001$) in esomeprazole-treated patients (96.0%; 95% CI 92.8, 99.1) than in placebo recipients (64.4%; 95% CI 56.8, 71.9). Esomeprazole was effective at preventing peptic ulcers in both *Helicobacter pylori*-positive and -negative patients (96.3% vs. 95.5% of patients ulcer-free, respectively); however, in the placebo group, the proportion of ulcer-free patients at 24 weeks was markedly lower among *H. pylori*-positive than -negative patients (59.7% vs. 69.9%). The NSAID type did not seem to affect the estimated ulcer-free rate with esomeprazole. Treatment with esomeprazole was well tolerated.

Conclusion
Esomeprazole 20 mg once daily is effective and safe in preventing ulcer recurrence in Japanese patients with a definite history of peptic ulcers who were taking an NSAID (ClinicalTrials.gov identifier: NCT00542789).

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for a range of common conditions such as low back pain, degenerative musculoskeletal diseases and rheumatic diseases. Despite their effectiveness in treating such conditions, data from Western populations show that continuous use of NSAIDs is an established risk factor for the development of gastrointestinal (GI) adverse events (AEs), ranging from upper GI symptoms such as heartburn and dyspepsia[1, 2] to peptic ulcer, which may lead to life-threatening complications such as bleeding or perforation.[3–5] Patients with a history of peptic ulcer bleeding are at the highest risk of NSAID-induced ulcer complications.[6, 7] Cyclo-oxygenase (COX)-2 selective inhibitors were developed in an attempt to circumvent the GI and cardiovascular AEs associated with nonselective NSAIDs, and although these agents have a better GI tolerability profile, they are still associated with an increased risk of upper GI complications in the general population.[8]

These findings demonstrating an increased risk of upper GI injury with NSAIDs in Western populations mirror those seen in Japanese individuals.[9, 10] Results of a survey conducted by the Japan Rheumatism Foundation, for example, showed that 15.5% of Japanese patients with rheumatoid arthritis who were treated with NSAIDs for 3 months or longer had gastric ulcers, and 1.9% had duodenal ulcers; these rates were 3.8–4.7 times higher than those in the general population.[11] In addition, among Japanese patients undergoing inpatient treatment for peptic ulcer bleeding, 18% were users of non-aspirin NSAIDs.[12]

Proton pump inhibitor (PPI) therapy is a recommended strategy for the treatment and prevention of NSAID-related GI AEs among at-risk patients,[13] and the efficacy and safety of esomeprazole in this setting is well documented in Western populations.[14–16] However, few published data are currently available to indicate whether similar efficacy and tolerability might be expected in the Japanese population. This study was therefore designed to assess the efficacy and tolerability of esomeprazole in Japanese patients with a history of peptic ulcer who were receiving daily, long-term NSAID therapy.

METHODS

Study design

This prospective, randomised, double-blind, parallel-group, placebo-controlled study (ClinicalTrials.gov identifier: NCT00542789; AstraZeneca study code: D961HC00001) was conducted at 57 institutions in Japan. The study design is presented in Figure 1. The study was approved by an independent review board at each institution. Written informed consent was obtained from all patients before commencement of the study. The first patient was enrolled on 27 August 2007 and the last patient completed the trial on 17 February 2009. The study procedures were performed in accordance with the ethical principles of the Declaration of Helsinki, ICH/Good Clinical Practice, and the applicable regulatory requirements in Japan [Good Clinical Practice for Trials on Drugs (Ministry of Health, Labour and Welfare) Ordinance No. 28, 1997].

Patients and treatment

Japanese adult patients (aged $\geq$20 years) with a history of peptic ulcer (endoscopically confirmed scar within 2 weeks before randomisation, or with documented previous endoscopically verified ulcer) who also required daily ($\geq$5 days per week), long-term NSAID therapy for a medically diagnosed chronic inflammatory condition

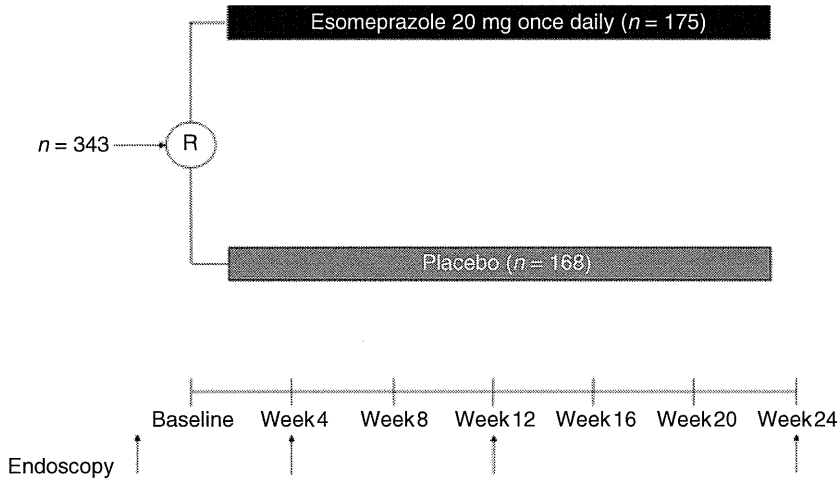

Figure 1 | Study design. R, randomisation.

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were included in this 24-week study. Patients receiving any type of oral NSAID, including nonselective agents, aspirin ($\geq$1000 mg/day, when used alone), and COX-2 selective inhibitors, were eligible for inclusion. The NSAID use was expected to be at a constant dose for the duration of the study. Additional oral or topical NSAID therapy was permitted, at the discretion of the investigator (when aspirin was used as an additional NSAID the daily dose was required to be $\geq$325 mg). Concomitant use of corticosteroids and disease-modifying antirheumatic drugs was permitted provided the drugs were in use at a constant dose for at least 4 weeks before randomisation (and the dose was expected to be constant for the duration of the study). Patients already receiving mucosal protectants were eligible for inclusion provided the investigator considered that such therapy needed to be taken continuously during the study, and at a constant dose.

Patients were excluded from the study if they had: visible ulcer at baseline endoscopy; history of gastric surgery (with the exception of simple ulcer closure), severe liver or renal diseases; history of malignant diseases; current or past evidence of defined conditions including, but not limited to, gastric/oesophageal disorders, uncontrolled diabetes mellitus, severe cardiovascular or cerebral vascular diseases; or had any significant alarm symptoms within 24 weeks before randomisation. Concomitant treatment with other PPIs, H_2-receptor antagonists, *Helicobacter pylori* eradication therapy or anticoagulants/antiplatelets (include aspirin <325 mg/day) was not allowed. Both *H. pylori*-negative and -positive patients were eligible for inclusion in the study; presence of *H. pylori* infection was determined by a locally validated serological test (IgG antibody test [E Plate 'Eiken' *H. pylori* Antibody[17]]). Genetic tests (which were performed with written informed consent from participating patients) were also completed to determine patients' cytochrome P450 (CYP) 2C19 genotype; based on the result of this test, patients were classified as 'extensive metabolisers' (homo- and hetero- types) or 'poor metabolisers' (patients were eligible for inclusion irrespective of CYP2C19 status). Such tests were completed by a central laboratory using the invader method (Mitsubishi Chemical Medience Corporation, Tokyo, Japan).

Eligible patients were randomised sequentially in a 1:1 ratio to 24 weeks of double-blind treatment with either esomeprazole 20 mg once daily (od) or matching placebo, according to a computer-generated random assignment programme. The appearance, packaging and labelling of the esomeprazole and placebo capsules were identical to maintain blinding. One capsule of esomeprazole 20 mg or placebo was taken daily, after breakfast, for 24 weeks. Compliance with study treatment was assessed by counting returned unused capsules at clinic visits; acceptable compliance was defined as intake of 75% or more of prescribed study medication. Compliance with daily NSAID therapy was recorded using daily patient diaries.

Outcomes

The primary objective was to assess the efficacy of esomeprazole 20 mg od, compared with placebo, by evaluating peptic ulcer rates during the treatment period of 24 weeks. Prespecified subgroup analyses of ulcer-free rates according to patient demographic and clinical characteristics, including gender, age, *H. pylori* status, CYP2C19 metaboliser status, type of NSAID used (COX-2 selective versus nonselective), and use of corticosteroids and mucosal protectants, were conducted. An exploratory analysis on ulcer-free rates among those receiving celecoxib, etodolac or meloxicam was also conducted.

Secondary objectives included evaluation of ulcer-free rates at 4 and 12 weeks post-randomisation, and severity of gastric mucosal lesions at 4, 12 and 24 weeks of treatment (evaluated according to the modified LANZA score[18]). The presence and severity of prespecified dyspeptic symptoms after 4, 8, 12, 16, 20 and 24 weeks of treatment was also evaluated, based on a 1-week recall by patients (none, mild, moderate or severe). Six GI symptoms were evaluated: epigastric pain, stomach discomfort, feeling of abdominal fullness, nausea/vomiting, heartburn and anorexia.

Safety and tolerability evaluations included an assessment of AEs (spontaneously reported by patients, and in response to open questioning), clinical laboratory values (including haematology, clinical chemistry and urinalysis) and vital signs. Laboratory tests were completed by a central laboratory (Mitsubishi Chemical Medience Corporation). All AEs were evaluated by investigators in terms of maximum intensity (mild, moderate or severe), seriousness, outcome and possible causality with study medication. The occurrence or deterioration of endoscopic findings (i.e. ulcer or erosions) was not recorded as an AE given that such end points were included in the efficacy evaluation.

Statistical analyses

The estimated ulcer-free rate by the Kaplan–Meier method, based on time-to-event curves for the full analysis set (FAS), was the primary efficacy analysis.

Statistical comparisons were made using the log-rank test. The FAS population consisted of all randomised patients who took at least one dose of study medication and who did not have any active or current gastric or duodenal ulcers at baseline. Ulcer-free rates for each treatment group with two-sided 95% CIs were obtained using the Greenwood formula.[19] Supplementary efficacy analyses were completed according to a Central Evaluation Committee (Y.K. and H.M.), who were blinded to study treatments and independently reviewed each patient's endoscopic findings at baseline and throughout the study. Endoscopic evaluation of ulcer scarring at baseline and peptic ulcer throughout the study was performed according to the Sakita/Miwa classification (ulcers were defined as 'active stage' or 'healing stage').[20]

The observed ulcer-free rates at weeks 4, 12 and 24 (two-sided 95% CIs) were calculated for each treatment group, and compared using the χ^2 test. The modified LANZA scores at baseline and study end (shift table) were summarised for each treatment group using descriptive statistics.

Among patients who did not have prespecified dyspeptic symptoms at baseline, the proportion of patients with symptoms (i.e. mild, moderate or severe) at each time point post-randomisation was calculated for each treatment group. Likewise, for patients who had dyspeptic symptoms at baseline, the proportion of patients with no symptoms post-randomisation was calculated for each treatment group. Change of dyspeptic symptom findings between baseline and study end was indicated by shift tables.

Safety findings were evaluated descriptively for the safety analysis set, i.e. all patients who took at least one dose of study medication and for whom any post-dose data were available.

Sample-size calculation

Based on data from previous trials,[14] the cumulative proportion of ulcer-free patients at week 24 was assumed to be 95% and 85%, respectively, in the esomeprazole 20 mg od and placebo treatment arms. To achieve 80% power to detect a difference in the primary end point between the esomeprazole and placebo groups based on a log-rank test at the 0.05 significance level (two-sided), at least 158 patients would need to complete treatment in each group. Assuming 5% of patients would withdraw before completing 24 weeks of treatment, 170 patients would need to be randomised into each treatment group (340 patients in total).

RESULTS

Patients

A total of 1246 patients were enrolled, of whom 343 patients were randomised to treatment (esomeprazole, $n = 175$; placebo, $n = 168$). The main reason for failure to be randomised was study ineligibility, based on endoscopic findings. Of randomised patients, 286 completed the study (esomeprazole, $n = 140$; placebo, $n = 146$). The flow diagram of this study is presented in Figure 2.

The two treatment groups were well balanced with respect to demographic and clinical characteristics at baseline (Table 1). Most patients were women (61.0%, $n = 208$), and the mean age was 63.0 years. Over one-half of the patients had rheumatoid arthritis or osteoarthritis (52.2%, $n = 178$), and were positive for *H. pylori* infection (53.7%, $n = 183$). Around one-quarter of patients were CYP2C19 poor metabolisers (21.7%, $n = 72$), consistent with previously reported findings for the Japanese population.[21]

Overall, 94.8% of esomeprazole 20 mg od ($n = 164$) and 97.0% of placebo ($n = 163$) recipients were compliant with study medication. Review of patient diaries showed that nearly all patients (97.7%, $n = 333$) were compliant with daily NSAID treatment (96.0% of esomeprazole 20 mg od and 99.4% of placebo recipients). The most commonly used NSAIDs were loxoprofen (35.2%, $n = 120$), meloxicam (21.1%, $n = 72$) and etodolac (15.2%, $n = 52$), and the use of such agents was generally comparable for the two treatment groups. Celecoxib was used by a few patients (3.8%, $n = 13$). The majority of patients used only one NSAID (97.1% of esomeprazole 20 mg od and 96.4% of placebo recipients), and most used nonselective agents (76.9% and 82.7% respectively). Eleven patients (esomeprazole, $n = 6$; placebo, $n = 5$) who used multiple NSAIDs typically used nonselective agents in combination. Some 21.1% of patients ($n = 72$) used corticosteroids concomitantly, most commonly prednisolone (15.5%, $n = 53$). Use of corticosteroids was similar for the two treatment groups. Approximately 90% of patients ($n = 312$) also used mucosal protectant medications concomitantly defined as use at baseline and for at least 50% of the treatment period. The most commonly used agent was rebamipide (47.2%, $n = 161$). The placebo group showed a significantly higher usage of mucosal protectants compared with esomeprazole recipients [94.6% and 88.4%, respectively; $P = 0.04$ (χ^2 test)].

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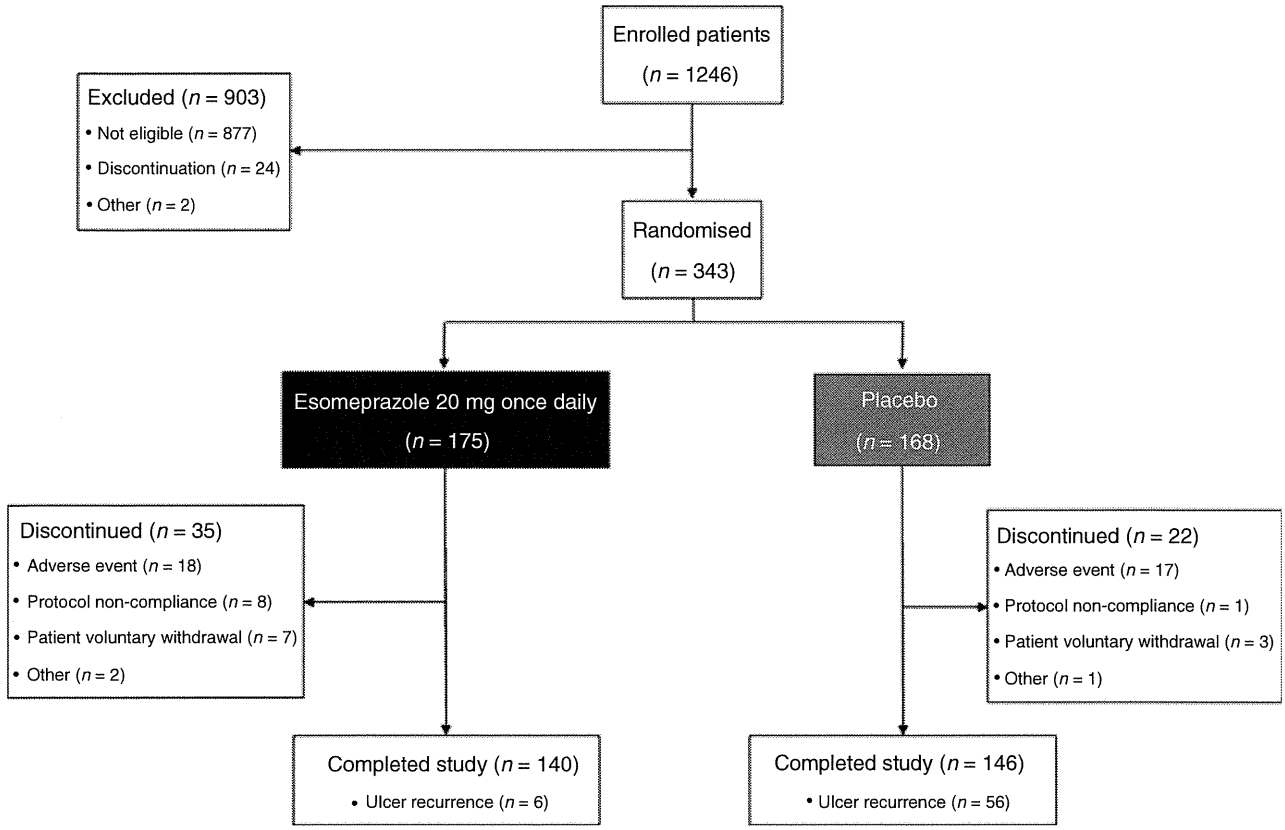

Figure 2 | Patient flow.

Peptic ulcer-free rates

Among the FAS population, the Kaplan–Meier estimated ulcer-free rate over the 24-week treatment period (primary end point) was significantly higher ($P < 0.001$, log-rank test) in the esomeprazole group (96.0%; 95% CI 92.8, 99.1) than in the placebo group (64.4%; 95% CI 56.8, 71.9) (Figure 3). Similar results were apparent for the efficacy analysis according to the Central Evaluation Committee [estimated ulcer-free rate: esomeprazole, 97.1% (95% CI 94.3, 99.9); placebo, 65.6% (95% CI 57.5, 73.7); $P < 0.001$, log-rank test]. The observed ulcer-free rate was also significantly higher for esomeprazole 20 mg od than for placebo at all time points (week 4: 99.4% vs. 79.2%; week 12: 97.1% vs. 70.8%; week 24: 96.5% vs. 66.7%; all $P < 0.001$, χ^2 test). Gastric ulcer developed most frequently during the study period (esomeprazole, $n = 5$; placebo, $n = 47$), followed by duodenal ulcer (esomeprazole, $n = 1$; placebo, $n = 6$) and combined gastric and duodenal ulcer (placebo, $n = 3$). Sub-analysis indicated the mean (±s.d.) size of the peptic ulcer was similar between the two treatments (6.7 ± 4.5 mm and 7.2 ± 5.4 mm, respectively, for the esomeprazole and placebo groups). Additional analysis showed that around half of patients with recurrent ulcer were symptomatic [esomeprazole, 50.0% (3 of 6); placebo, 51.8% (29 of 56)], the most common symptoms being epigastric pain and stomach discomfort.

Estimated peptic ulcer-free rates by subgroup (gender, age category, *H. pylori* status, type of NSAID, use of corticosteroids and mucosal protectants and CYP2C19 status) at week 24 are presented in Table 2. Esomeprazole appeared to be similarly effective at preventing peptic ulcers irrespective of patient gender, age category or *H. pylori* status. In the placebo group, the observed proportion of ulcer-free patients at 24 weeks was somewhat lower in *H. pylori*-positive than -negative patients (59.7% vs. 69.9%), and those aged ≥75 years appeared to be particularly at risk of ulcer recurrence. The type of NSAID used did not seem to substantially impact the estimated ulcer-free rate for esomeprazole, which was also consistently effective in preventing the recurrence of peptic ulcers in all CYP2C19 genotype subgroups.

Severity of gastric mucosal lesions

In the FAS population, more patients [31.9% (53 of 166)] in the esomeprazole 20 mg od group experienced

Table 1 | Baseline characteristics of patients (full analysis set*)

	Esomeprazole 20 mg once daily (n = 173)	Placebo (n = 168)
Women	108 (62.4)	100 (59.5)
Mean age, years (s.d.)	63.6 (12.2)	62.4 (12.3)
Arthritic condition		
Rheumatoid arthritis	54 (31.2)	48 (28.6)
Osteoarthritis	44 (25.4)	32 (19.0)
Helicobacter pylori-positive	97 (56.1)	86 (51.2)
Gastric mucosal atrophy†	39 (22.5)	33 (19.6)
CYP2C19 genotype‡		
Poor metaboliser	35 (20.2)	39 (23.2)
Heterozygous extensive metaboliser	80 (46.2)	74 (44.0)
Homozygous extensive metaboliser	58 (33.5)	54 (32.1)

CYP2C19, cytochrome P450 isoenzyme 2C19; s.d., standard deviation.

All values are presented as n (%) patients, unless otherwise stated.

* Patients who were randomised to treatment and who took at least one dose of study medication and who had no active/current peptic ulcers at the baseline endoscopy.

† According to the Kimura and Takemoto classification.[32]

‡ CYP2C19 metaboliser status was unknown for one patient in the placebo group.

an improvement in modified LANZA score after 24 weeks' treatment than in the placebo group (17.0% [28 of 165]), and fewer esomeprazole recipients had some worsening of LANZA score [10.8% (18 of 166)] relative to those in the placebo group [47.9% (79 of 165)] (Table 3).

Dyspeptic symptoms

Very few patients in both the esomeprazole 20 mg od and placebo groups had dyspeptic symptoms, either at baseline or during the course of the study. Severe symptoms were rare. At study end, >80% of patients had no dyspeptic symptoms; the proportion of patients with no such symptoms was numerically greater in esomeprazole-treated patients than those who received placebo (Table 4).

Safety and tolerability

The mean duration of exposure (±s.d.) was 142.3 ± 52.1 days for esomeprazole 20 mg od and 116.0 ± 63.8 days for placebo. No deaths occurred during the study. The frequency of AEs was similar for the esomeprazole 20 mg od and placebo treatment groups (77.5% and 73.8% of patients, respectively) (Table 5); most of these events occurred in the GI system organ class and were of mild or moderate intensity. The AEs considered possibly related to study treatment, as judged by the investigator, were much less common (13.9% and 16.1% for the esomeprazole 20 mg od and placebo groups, respectively) (Table 5).

There were three serious AEs (SAEs) in three patients in the esomeprazole treatment group where the investigator considered that there was a possible relationship to study treatment: pyelonephritis, gastric cancer and lumbar spinal canal stenosis. The severity of the three SAEs was rated as mild-to-moderate in intensity.

In total, 35 patients discontinued study treatment due to AEs: 18 patients (10.4%) in the esomeprazole 20 mg od group and 17 patients (10.1%) in the placebo group (an additional 4 placebo-treated patients also discontinued with AEs, but were not included as they also had recurrence of ulcer as the reason for study withdrawal).

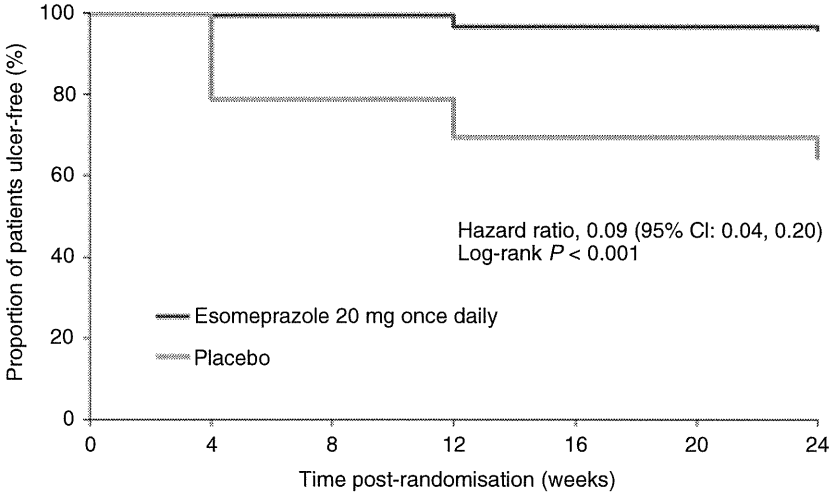

Figure 3 | Kaplan–Meier estimates of sustained ulcer-free status throughout 24 weeks of treatment (full analysis set).

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Table 2 | Kaplan–Meier-estimated peptic ulcer-free rates (95% CI) in patient subgroups at week 24 (full analysis set*)

	Esomeprazole 20 mg once daily (n = 173)		Placebo (n = 168)	
	n	Ulcer-free rate (95% CI)	n	Ulcer-free rate (95% CI)
Sex				
Men	65	100.0% (100.0, 100.0)	68	62.6% (50.6, 74.5)
Women	108	93.6% (88.6, 98.6)	100	65.9% (56.2, 75.6)
Age, years				
≤64	78	97.2% (93.4, 100.0)	91	63.2% (52.8,73.6)
≥65 to ≤74	59	96.2% (90.9, 100.0)	54	71.0% (58.5, 83.4)
≥75	36	92.9% (83.3, 100.0)	23	52.6% (30.9, 74.3)
Helicobacter pylori status				
Positive	97	96.3% (92.2, 100.0)	86	59.7% (49.0, 70.5)
Negative	76	95.5% (90.6, 100.0)	82	69.9% (59.6, 80.3)
Type of NSAID				
Celecoxib	4	100.0% (100.0, 100.0)	9	44.4% (12.0, 76.9)
Etodolac or meloxicam	67	94.5% (88.5, 100.0)	54	67.2% (54.3, 80.0)
Nonselective†	102	96.8% (93.1, 100.0)	105	64.4% (54.7, 74.1)
Corticosteroid use				
Yes	36	88.1% (77.2, 99.1)	36	88.1% (77.1, 99.2)
No	137	98.4% (96.1, 100.0)	132	57.9% (49.1, 66.7)
Mucosal protectant use				
Yes	153	96.1% (92.7, 99.4)	159	65.7% (58.0, 73.4)
No	20	95.0% (85.4,100.0)	9	44.4% (12.0, 76.9)
CYP2C19 genotype				
Poor metaboliser	35	96.8% (90.6, 100.0)	39	69.1% (53.7, 84.5)
Heterozygous extensive metaboliser	80	95.7% (91.0, 100.0)	74	57.2% (45.5, 68.9)
Homozygous extensive metaboliser	58	95.8% (90.2, 100.0)	54	71.2% (58.8, 83.5)
Unknown	0		1	100.0% (100.0, 100.0)

CYP2C19, cytochrome P450 isoenzyme 2C19; NSAID, nonsteroidal anti-inflammatory drug.

* Patients who were randomised to treatment and who took at least one dose of study medication and who had no active/current peptic ulcers at the baseline endoscopy.

† Including users of aspirin (≥1000 mg/day).

Table 3 | Shift analysis of modified LANZA score after 24 weeks' treatment with esomeprazole 20 mg once daily or placebo, stratified by modified LANZA score at baseline (full analysis set)

	Esomeprazole 20 mg once daily					Placebo				
	Baseline					Baseline				
Study end	0	+1	+2	+3	+4	0	+1	+2	+3	+4
0	78	9	26	3	1	41	2	19	0	0
+1	1	5	6	4	0	8	0	4	0	0
+2	9	1	10	3	1	12	4	14	3	0
+3	1	0	1	0	0	0	1	1	3	0
+4	3	0	1	1	2	29	7	11	6	0

More placebo recipients discontinued treatment due to GI disorders (7.7%) than esomeprazole-treated patients (2.9%) (P = 0.045, χ^2 test).

Clinical laboratory evaluations and assessment of vital signs raised no safety concerns (data not shown).

DISCUSSION

To our knowledge, this is the first placebo-controlled, randomised study to evaluate the use of esomeprazole in Japanese patients with a history of peptic ulcer and who were receiving long-term, daily oral NSAID therapy.