Longterm Retention Rate and Risk Factor for Discontinuation Due to Insufficient Efficacy and Adverse Events in Japanese Patients with Rheumatoid Arthritis Receiving Etanercept Therapy

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ABSTRACT. ***Objective.*** Assessing retention rate and risk factor for drug discontinuation is important for drug evaluation. We examined a 3-year retention rate and the risk factor for discontinuation due to insufficient efficacy (IE) and adverse events (AE) in Japanese patients with rheumatoid arthritis (RA) who are receiving etanercept (ETN).

Methods. Data were collected from 588 patients treated with ETN as a first biologic from the Tsurumai Biologics Communication Registry. Baseline characteristics for the incidence of both IE and AE were analyzed using the Cox proportional-hazards regression model. Patients were divided into groups based on age and concomitant methotrexate (MTX). Drug retention rates were calculated using the Kaplan-Meier method and compared among groups using the log-rank test.

Results. ETN monotherapy without concomitant MTX [MTX(–)] was significantly related to a higher incidence of discontinuation due to IE [hazard ratio (HR) = 2.226, 95% CI 1.363–3.634]. Older age and MTX(–) were significantly related to a higher incidence of discontinuation due to AE [HR = 1.040, 1.746, 95% CI 1.020–1.060, 1.103–2.763, respectively]. The MTX(–)/≥ 65 years group had the lowest retention rate ($p < 0.001$). The discontinuation rate due to IE was lower in the MTX(+)/< 65 years group compared to < 65 years/MTX(–), ≥ 65 years/MTX(–) group ($p = 0.006$, $p < 0.001$, respectively). The discontinuation rate due to AE was highest in the MTX(–)/≥ 65 years group ($p < 0.001$).

Conclusion. Our findings suggest that the risk of discontinuation due to IE was high in the patients who did not use concomitant MTX and that the risk of discontinuation due to AE was high in elderly patients who did not use concomitant MTX. (First Release July 15 2014; J Rheumatol 2014; 41:1583–9; doi:10.3899/jrheum.130901)

Key Indexing Terms:
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Biologics play a pivotal role in the treatment of rheumatoid arthritis (RA). In Japan, infliximab, etanercept (ETN), adalimumab, tocilizumab, abatacept, and golimumab have been approved and postmarket surveillance (PMS) conducted. Reports of clinical efficacy also exist[1,2]. Yet, evaluation of the safety and longterm efficacy of biologics requires large-scale, longterm followup data. To this end, we developed a database of patients with RA who were treated with biologics (Tsurumai Biologics Communication Registry; TBCR) in October 2008 to document the clinical course of these patients[3,4,5].

Patients with RA discontinue biologics for several reasons, including lack of efficacy, adverse events (AE), and economic reasons. Given that longterm retention to drug therapy reflects a good balance between drug efficacy and tolerability, assessing the retention rate and reasons for discontinuation in large populations is important for drug evaluation.

Older patients with RA are often treated with biologics in clinical settings, but are at greater risk for infections compared to younger patients. This highlights the need to weigh both the advantages and disadvantages of biologics use.

ETN is a soluble human tumor necrosis factor (TNF)-α receptor fusion protein that is effective in patients who fail to respond to disease-modifying antirheumatic drugs such as methotrexate (MTX), and shows greater efficacy when combined with MTX than when used alone[6]. The effect of concomitant MTX on ETN persistence in RA has been examined in a number of studies[7,8,9]. Five-year level of adherence to therapy for patients receiving ETN with concomitant MTX was 65% compared with 53% for receiving ETN alone[8].

Several have reported on the long-term efficacy and safety of ETN from the West, and PMS and Sakai, *et al*[10] have published large-scale surveys in Japan[1]. However, a survey on the 3-year retention rate or factors that influence discontinuation has not yet been reported, to our knowledge.

Our study aimed to examine the 3-year retention rate to ETN therapy and the risk factor for discontinuation due to insufficient efficacy (IE) and AE based on TBCR data.

MATERIALS AND METHODS

TBCR. A new registry of patients with RA starting treatment with biologics in 2008 was developed to explore the longterm prognosis of treatment with biologics in clinical practice[3]. Data were collected prospectively from 2008, as well as retrospectively for patients who had been treated with biologics up until 2008. Our study was approved by the Ethics Committee of Nagoya University, School of Medicine and other associated hospitals. Of the 2072 patients registered in the TBCR as of October 2011, 883 initiated treatment with ETN. The 588 patients who could be followed for more than 2 years were enrolled in this study. All patients met the 1987 ACR classification criteria for RA.

Baseline data and followup. We recorded age at baseline, sex, disease duration, Steinbrocker stage of joint destruction, Steinbrocker functional class, DAS28-CRP disease activity score, and concomitant treatment with methotrexate (MTX) or prednisolone (PSL). The beginning of the observation period was the date of initiating ETN therapy. Observation was stopped either at 3 years after the start of ETN, or when ETN was discontinued for any reason. For cases of discontinuation, the reasons were recorded (e.g., AE, lack of efficacy, or personal reasons). For discontinuation due to lack of efficacy, we did not distinguish between primary and secondary failure. Followup was performed by rheumatologists during regular visits at each institute. The mean ± SD followup period was 3.09 ± 1.83 years.

Statistical analysis. To examine baseline characteristics by age and initiation period of biologics, retrospectively registered patients were divided into 3 groups based on age tertiles: ≤ 52 years (n = 192), 53 to 64 years (n = 208), and ≥ 65 years (n = 188) groups. Differences among groups were analyzed with the Kruskal-Wallis test for continuous variables and the chi-squared test for categorical variables. One-way ANOVA was used to compare DAS28-CRP differences among groups. Drug retention rates were calculated using the Kaplan-Meier method and compared among groups using the log-rank test. Adjustment was made for variables such as age, sex, disease duration, Steinbrocker stage, Steinbrocker class, concomitant use of PSL, and concomitant dosage of PSL. Factors associated with the incidence of discontinuation due to IE and AE were analyzed using the Cox proportional hazards regression model with the backward stepwise method. The validity of the proportional hazards assumption was confirmed by the log-log survival function. Missing data were identified in a total of 40 patients from several variables, and these were removed from the Cox proportional hazards model. All data were analyzed using SPSS version 19.0 (IBM). $P < 0.05$ was considered statistically significant.

RESULTS

A total of 588 patients (1819 patient-yrs) from 13 facilities participated in the study. The mean age (SD) and mean disease duration (SD) were 59.7 (14.3) and 11.0 (9.8) years, respectively. Baseline characteristics for each age group are shown in Table 1. Significant differences between age groups were found in sex, disease duration, stage of joint damage, class of dysfunction, concomitant MTX use, concomitant PSL use and PSL dosage, and DAS28-CRP at initiation of ETN therapy. Patients who were ≤ 52 years old had shorter disease duration, less progression of joint damage, less physical dysfunction, and lower disease activity. The proportion of patients who had a disease duration of < 2 years was high in the ≤ 52 years group, although no significant difference was observed between the groups. The proportion of concomitant MTX use was higher in the ≤ 52 years old group, but no difference was observed between groups for dosage. A total of 323 patients continued ETN therapy for 3 years; 85 discontinued because of IE, 85 because of AE, and 24 for other reasons.

We examined factors related to both IE and AE (Table 2). When the multivariate analysis was applied, ETN monotherapy without concomitant MTX use [MTX(–)] was significantly related to a higher incidence of discontinuation due to IE [hazard ratio (HR) = 2.226, 95% CI 1.363–3.634]. Disease duration was significantly related to discontinuation due to IE, but the correlation was weak (HR = 0.969, 95% CI 0.942–0.996; Table 2). The older age and MTX(–) were significantly related to a higher incidence of discontinuation due to AE (HR = 1.040, 1.746, 95% CI 1.020–1.060, 1.103–2.763, respectively; Table 2).

Table 1. Differences in baseline patient characteristics by age at initiation of etanercept. Except where indicated otherwise, values are mean (SD).

Variables	All Ages, n = 588	Young (≤ 52 yrs), n = 192	Middle-aged (53–64 yrs), n = 208	Elderly (≥ 65 yrs), n = 188	p
Age, yrs	56.5 (14.2)	39.8 (9.4)	58.8 (3.5)	71.1 (4.9)	
Women, %	83.3	89.6	84.0	76.1	0.002
Disease duration, yrs*	8.9 (4.0–16.0)	7.0 (3.0–13.0)	10.0 (4.0–16.0)	9.0 (4.0–17.0)	0.003
Disease duration ≤ 2 yrs, %	19.5	24.5	16.8	17.2	n.s.
Steinbrocker stage, %					0.001
I	9.6	15.9	8.3	4.2	
II	15.7	15.3	12.5	19.8	
III	32.5	35.5	30.7	31.1	
IV	42.3	33.3	48.5	44.9	
Steinbrocker class, %					< 0.001
I	22.5	38.4	18.6	10.2	
II	33.6	36.8	35.7	27.8	
III	34.3	17.8	34.2	51.7	
IV	9.6	7	11.5	10.3	
RF-positive, %	88.6	83.7	90.0	92.0	n.s.
MTX use, %	65.7	74.5	65.9	55.2	0.002
MTX dosage, mg/wk*	8.0 (6.0–8.0)	8.0 (6.0–8.0)	8.0 (6.0–8.0)	8.0 (6.0–8.0)	n.s.
PSL use, %	73.2	64.9	72.0	84.1	0.015
≤ 5 mg	79.4	82.5	74.6	81.2	n.s.
> 5 mg	20.6	17.5	25.4	18.8	
PSL dosage, mg/day	5.1 (2.0)	4.5 (2.0)	5.6 (2.2)	5.1 (1.8)	0.007
DAS28-CRP	4.94 (1.05)	4.55 (1.07)	5.16 (1.03)	5.11 (0.95)	< 0.001

*Median (interquartile range). P values for continuous variables were determined with the Kruskal-Wallis test. P values for categorical variables were determined with the chi-square test. One-way ANOVA was used to compare DAS28-CRP differences among groups. DAS28-CRP: Disease Activity Score in 28 joints based on C-reactive protein levels with 4 variables; MTX: methotrexate; PSL: prednisolone; RF: rheumatoid factor; n.s.: not significant.

Table 2. Factors associated with insufficient efficacy and adverse events within 3 years from initiation of etanercept*.

Factors	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Insufficient efficacy				
Age, yrs	1.013 (0.996–1.030)	0.147	–	–
Sex, male vs female	1.267 (0.695–2.311)	0.439	–	–
Disease duration, yrs	0.980 (0.954–1.006)	0.133	0.969 (0.942–0.996)	0.024
Stage III or IV (vs stage I or II)	0.855 (0.507–1.442)	0.557	–	–
Class III and IV (vs class I or II)	1.416 (0.894–2.241)	0.138	–	–
MTX no use (vs use)	2.105 (1.308–3.385)	0.002	2.226 (1.363–3.634)	0.001
PSL no use (vs use)	1.396 (0.847–2.301)	0.191	–	–
PSL > 5 mg (vs ≤ 5 mg)	1.284 (0.589–2.798)	0.530	–	–
Adverse events				
Age, yrs	1.042 (1.023–1.062)	< 0.001	1.040 (1.020–1.060)	< 0.001
Sex, male vs female	1.036 (0.560–1.916)	0.911	–	–
Disease duration, yrs	1.017 (0.996–1.038)	0.122	–	–
Stage III or IV (vs stage I or II)	1.266 (0.721–2.223)	0.412	–	–
Class III and IV (vs class I or II)	1.857 (1.183–2.917)	0.007	–	–
MTX no use (vs use)	1.955 (1.239–3.086)	0.004	1.746 (1.103–2.763)	0.017
PSL no use (vs use)	0.916 (0.582–1.442)	0.705	–	–
PSL > 5 mg (vs ≤ 5 mg)	1.182 (0.544–2.571)	0.672	–	–

*Cox proportial-hazards regression model, adjusted for the variables included in the table. MTX: methotrexate; PSL: prednisolone.

Kaplan-Meier curves for each age group are shown in Figure 1. The retention rate for all ages was 72% at 2 years and 67% at 3 years. The ≥ 65 years group had a lower retention rate compared to the other 2 groups ($p < 0.001$, log-rank test). No significant difference was observed between the ≤ 52 years and the groups 53 to 64 years.

Patients were further divided into groups < 65 years and ≥ 65 years of age, and retention rates were compared with

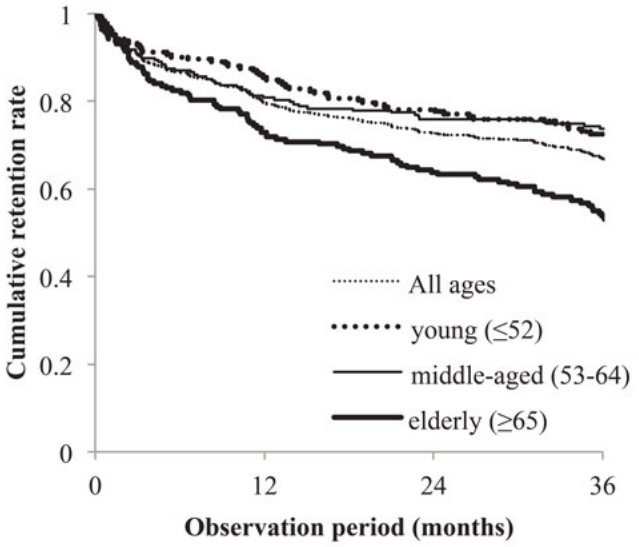

Figure 1. Kaplan-Meier curves for time to discontinuation of etanercept for the various age groups (all ages, young, middle-aged, elderly). Retention rates among age groups (young, middle-aged, elderly) were compared using the log-rank test. Adjustment was made for variables such as age, sex, disease duration, Steinbrocker stage, Steinbrocker class, concomitant use of prednisolone (PSL), and concomitant dosage of PSL.

respect to concomitant MTX use [MTX(+)]. Baseline characteristics for each age group are shown in Table 3. Significant differences between age groups were found in sex, stage of joint damage, class of dysfunction, MTX(+), and PSL(+) at first administration of biologics. The proportion of MTX(+) was higher in the < 65 years group than in the ≥ 65 years group, but no difference in dosage was found between the groups.

Kaplan-Meier curves for each group are shown in Figure 2A. The ≥ 65 years/MTX(–) group had the lowest retention rate ($p < 0.001$, log-rank test). No significant difference was observed between the ≥ 65 years/MTX(+) group and the < 65 years/MTX(–), and the ≥ 65 years/MTX(+) group and < 65 years/MTX(+) groups ($p = 0.086$, $p = 0.107$, respectively, log-rank test; Figure 2A). Kaplan-Meier curves for patients who discontinued because of IE and AE are shown in Figures 2B and 2C. The discontinuation rate due to IE was lower in the < 65 years/MTX(+) group compared to the < 65 years/MTX(–), and the ≥ 65 years/MTX(–) groups ($p = 0.006$, $p < 0.001$, respectively, log-rank test), but did not differ with that of the ≥ 65 years/MTX(+) group ($p = 0.680$, log-rank test; Figure 2B). The cumulative incidence rate of AE leading to discontinuation was high in the ≥ 65 years/MTX(–) group and low in the < 65 years/MTX(+) group ($p < 0.001$, log-rank test). No difference was found between the ≥ 65 years/MTX(+) and < 65 years/MTX(–) groups (Figure 2C).

Table 3. Differences in baseline patient characteristics by age (65 years) and concomitant MTX use at initiation of etanercept.

Variables	< 65 yrs/MTX(–), n = 174	< 65 yrs/MTX(+), n = 226	≥ 65 yrs/MTX(–), n = 114	≥ 65 yrs/MTX(+), n = 74	p
Age, yrs	50.7 (12.0)	48.9 (11.7)	71.2 (4.7)	71.0 (5.3)	–
Women, %	85.5	87.6	76.6	75.3	0.014
Disease duration, yrs*	9.0 (4.0–17.0)	8.0 (2.8–13.0)	10.0 (4.0–18.0)	8.5 (4.0–15.0)	0.035
Disease duration ≤ 2 yrs, %	14.6	25	15.7	19.4	n.s.
Steinbrocker stage, %					0.004
I	11.9	12.1	3.0	6.0	
II	8.8	17.7	21.0	17.9	
III	33.8	32.6	24.0	41.8	
IV	45.6	37.7	52.0	34.3	
Steinbrocker class, %					< 0.001
I	21.8	32.9	3.8	19.4	
II	33.3	38.4	25	31.9	
III	29.7	23.7	56.7	44.5	
IV	15.2	5	14.5	4.2	
RF-positive, %	92	81.4	94.4	87.9	n.s.
MTX dosage, mg/wk*	–	8.0 (6.0–8.0)	–	8.0 (6.0–8.0)	–
PSL use, %	75.9	65.4	87.8	80.5	0.019
≤ 5 mg	65.9	84.3	75.0	87.9	< 0.001
> 5 mg	34.1	15.7	25.0	12.1	
PSL dosage, mg/day	4.1 (3.2)	3.2 (2.8)	4.8 (2.3)	3.8 (2.6)	0.007
DAS28-CRP	5.19 (1.10)	4.72 (1.06)	5.23 (1.09)	4.99 (0.79)	0.009

Except where indicated otherwise, values are mean (SD). *Median (interquartile range). P values for continuous variables were determined with the Kruskal-Wallis test. P values for categorical variables were determined with the chi-square test. One-way ANOVA was used to compare DAS28-CRP differences among groups. DAS28-CRP: Disease Activity Score in 28 joints based on C-reactive protein levels with 4 variables; MTX: methotrexate; PSL: prednisolone; RF: rheumatoid factor; n.s.: not significant.

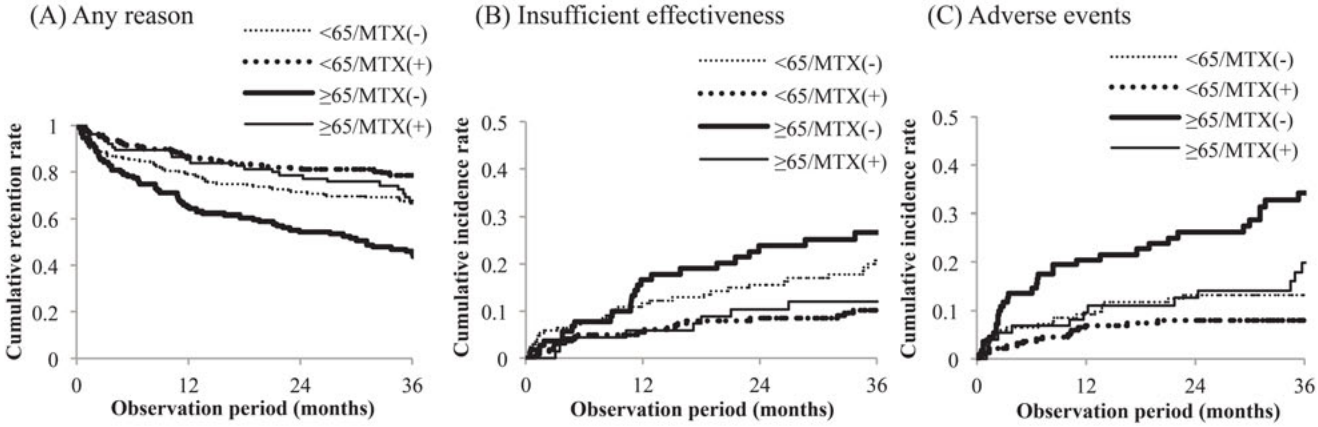

Figure 2. Kaplan-Meier curves for time to discontinuation of etanercept. Withdrawal for any reason (A), insufficient efficacy (B), and adverse events (C) are presented. Drug retention rates among groups [< 65 years/MTX(-), < 65 years/MTX(+), ≥ 65 years/MTX(-), ≥ 65 years/MTX(+)] were compared using the log-rank test. Adjustment was made for variables such as age, sex, disease duration, Steinbrocker stage, Steinbrocker class, concomitant use of prednisolone (PSL), and concomitant dosage of PSL. MTX: methotrexate.

AE leading to discontinuation within 3 years are summarized in Table 4. Regardless of age, infections were the most common reason for discontinuation in the MTX(–) groups, and compared to MTX(+) groups, the rates of occurrence were higher (Table 4).

DISCUSSION

In our study, we examined the retention rate to ETN therapy among TBCR-registered patients according to age, and found that patients with RA aged ≥ 65 years had a significantly lower retention rate and proportion of concomitant MTX use compared to the other age groups. One reason was a high discontinuation rate due to AE among elderly patients who underwent ETN therapy without concomitant MTX use.

A number of studies have reported on the rate of retention to ETN therapy[8,11,12,13]. In the DANBIO registry, the 2-year retention rate for 425 patients administered ETN was 56%[11]. In the Italian GISEA registry, the 4-year retention rate for 311 patients administered ETN was 51%[12]. In the Swiss Clinical Quality Management registry, the 2-year retention rate of 887 patients administered ETN was 65%, and the rate of discontinuation due to AE was comparable to that due to lack of efficacy[13]. In a Swedish study, 5-year retention rates were 65% with concomitant MTX use and 53% with ETN monotherapy; the discontinuation rate due to AE was low with concomitant MTX use[8]. In our study, the overall retention rates were 72% at 2 years and 67% at 3 years, which are comparable to those reported in previous studies. Patients aged < 65 years showed high retention rates of more than 70% at 3 years. While rates of discontinuation due to AE and IE were comparable overall, discontinuation due to AE was more frequent than that due to IE in patients aged ≥ 65 years without concomitant MTX use compared with other groups.

Cox's proportional hazards regression analysis revealed that ETN monotherapy without concomitant MTX use was a risk factor for discontinuation due to insufficient efficacy, while being of older age and not using concomitant MTX were risk factors for discontinuation due to AE. One previous study reported that older age is a risk factor for the discontinuation of biological drug products due to AE[14].

Table 4. Adverse events within 3 years of initiation of biologics. Values are mean (SD).

Reason for Discontinuation	< 65 Years		≥ 65 Years	
	MTX(+)	MTX(–)	MTX(+)	MTX(–)
Infection	3 (21.5)	9 (47.4)	3 (18.8)	16 (44.4)
Pulmonary diseases (except infection)	2 (14.3)	1 (5.2)	1 (6.2)	2 (5.6)
Disease of skin and subcutaneous tissue	1 (7.1)	4 (21.1)	0	2 (5.6)
Malignancy	1 (7.1)	2 (10.5)	2 (12.5)	2 (5.6)
Others	7 (50.0)	3 (15.8)	10 (62.5)	14 (38.8)
All categories	14 (100.0)	19 (100.0)	16 (100.0)	36 (100.0)

MTX: methotrexate.

Further, discontinuation of TNF inhibitors is reportedly more likely given that the risk of infections increases in the elderly[15,16]. In contrast, in a study by the British Society for Rheumatology Biologics Register, although the incidence of severe infections increased with age, the risk of developing an infection was reported to be no different between patients using TNF drugs and those using nonbiologic disease-modifying antirheumatic drugs[17]. Moreover, Fleischmann reported that for patients with RA (as well as psoriatic arthritis or ankylosing spondylitis) undergoing ETN therapy, the incidence of AE was similar for patients aged < 65 years and those aged ≥ 65 years[18].

In our study, discontinuation due to infections was frequent in patients ≥ 65 years/MTX(–), but relatively infrequent in patients ≥ 65 years/MTX(+). These results suggest that, in addition to age, concomitant MTX use may be related to fewer AE. MTX use in combination with anti-TNF agents reportedly leads to a better retention rate than do anti-TNF agents used alone[7,19]. In the Japanese PMS study of ETN, not using MTX increased the risk of developing serious infections[1]. Soliman, *et al* reported that, not only were these patients less likely to stop because of inefficacy, they were also less likely to experience AE leading to drug discontinuation. However, they acknowledge that the reasons for this are unclear[20]. On the other hand, the Registry of Japanese Patients with RA for Long-Term Safety database revealed that a mean dosage of > 8 mg MTX/week is an independent risk factor for serious infections[21]. Kristensen, *et al* noted that one reason concomitant MTX use is superior to monotherapy is that MTX is a more potent antirheumatic drug in itself. These authors also suggested, as another reason, that patients who cannot tolerate MTX possess undefined characteristics or comorbidities that predispose them to lower levels of retention to anti-TNF therapy[8]. In this study, it is unclear why some patients do not use MTX.

In our study, not using MTX increased the risk of discontinuation due to both IE and AE. Moreover, the mean dosage of MTX in those who used it was lower than that reported in Western cohorts. We suspect that the dosage was inadequate for control of disease activity. Indeed, in Japan, the maximum approved dosage of MTX for RA was 8 mg/week until February 2011. Another reason for the use of inadequate doses of MTX is the associated complications and AE, such as liver dysfunction. We speculate that the unstable disease activity may have resulted from inadequate MTX dosages, and patients may also have factors that increase the possibility of AE. Our findings are meaningful in that they are from a cohort in which disease activity was controlled using low MTX dosages.

In our survey, we found that use of PSL was significantly higher in elderly patients who did not take MTX. In addition, regardless of age, a higher proportion of patients in the non-MTX group had higher doses of PSL. In real clinical settings, we sometimes see cases for which, owing to an inability to administer MTX, PSL is administered to control disease activity at doses over 5 mg. Wolfe, *et al* have reported that PSL use influenced the incidence of severe pneumonia[22]. The Cox hazards regression model used in the present research found no significant association between PSL use (regardless of dose) and ETN discontinuation.

There are some limitations to our study worth noting. First, the multicenter study design raises the possibility of selection bias, because administration of ETN is at the discretion of rheumatologists at each institute. The degree of IE and AE, which was determined by each rheumatologist, was not defined clearly. Regarding the severity of AE required for discontinuation, in general, we assumed that the AE was severe enough when hospitalization was deemed necessary. However, the baseline characteristics of patients and the incidence of AE were comparable to the PMS of ETN in Japan[1]. Therefore, the effect of any selection bias is likely to be small. Second, the number of patients included in the analysis for determining the incidence of AE was small. Third, the observation period was limited. Further studies with larger study populations and longer followup periods are needed.

We compared retention rates to ETN therapy according to age using TBCR data. Our findings suggest that the risk of discontinuation due to IE was high in the patients who did not use concomitant MTX and that the risk of discontinuation due to AE was high in elderly patients who did not use concomitant MTX. In addition to more longterm data, more careful followup observations are necessary for elderly patients who cannot use MTX because of contraindications.

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