Clinical and radiologic analysis of on-demand use of etanercept for disease flares in patients with rheumatoid arthritis for 2 years: The RESUME study

A case–control study

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Abstract

To reduce costs of biological disease-modifying antirheumatic drugs (bDMARDs), we evaluated the efficacy of repeated etanercept (ETN) discontinuation and restarting in rheumatoid arthritis (RA) patients in a case–control study.

Thirty-one bDMARD-naive RA patients with moderate to high disease activity received ETN until low disease activity (LDA) was achieved, after which ETN was discontinued. Upon flaring, ETN was readministered with observation every 2 months for 2 years, and radiographically evaluated in comparison with a historical control group treated continuously with ETN. Statistical methods including Fisher exact test, analysis of variance (ANOVA), Kruskal–Wallis test, multiple regression analysis, and Student t test were conducted as appropriate.

Thirteen patients with inadequate response to ETN were withdrawn from the study, and 5 had no flare-up after ETN discontinuation. In the remaining 13 patients, ETN was used on-demand to maintain LDA. Multivariate analysis revealed that MTX was significantly correlated with ETN. All 13 patients achieved LDA at final follow-up. Although joint damage progressed in patients using ETN on-demand, structural damage progression in the on-demand group was not significantly different from that in controls.

On-demand use of ETN for flaring reduced disease activity but not structural damage in 50% of patients (though not significantly). However, inhibition of joint damage was achieved in 50% of patients after 2 years, supporting on-demand use of ETN as a treatment option for patients with RA who cannot afford bDMARD or targeted synthetic DMARD therapy.

Abbreviations: ANOVA = analysis of variance, bDMARDs = biological DMARDs, csDMARDs = conventional synthetic DMARDs, DAS28–ESR = Disease Activity Score–28–erythrocyte sedimentation rate, DMARDs = disease-modifying antirheumatic drugs, ETN = etanercept, EULAR = European League Against Rheumatism, IFX = infliximab, LDA = low disease activity, mTSS = modified total Sharp score, MTX = methotrexate, OR = odds ratio, RA = rheumatoid arthritis, tsDMARDs = targeted synthetic DMARDs.

Keywords: discontinuation, disease flare, etanercept, rheumatoid arthritis, structural damage

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1. Introduction

Successful treatment with synthetic and biological disease-modifying antirheumatic drugs (DMARDs) in line with the concept of “treat to target” has been shown to prevent joint damage and physical disability in patients with rheumatoid arthritis (RA).[1–3] To achieve treatment targets, use of biological DMARDs (bDMARDs) should be considered, as significant evidence of their efficacy has been demonstrated in recent years.[2,3] Upon achievement of treatment targets and persistent remission, tapering of bDMARDs or dose reduction of conventional synthetic DMARDs (csDMARDs) should be considered according to European League Against Rheumatism (EULAR) recommendations.[3]

One reason to consider tapering bDMARDs is their high cost, both at a national level as well as for patients. In the United States, the total annual cost for the treatment of RA has increased threefold since the introduction of bDMARDs.[4] Among other arguments for the tapering of bDMARDs, Sokka et al.[5] reported that the treatment target of remission/low disease activity (LDA) and good functional status can be reached in RA patients using expensive as well as less-expensive antirheumatic drugs. However, in the BeSt trial, most aggressive treatment arm with use of infliximab (IFX) achieved significantly better quality of life, although treatment costs were prohibitive. However, the authors suggested that these costs would be compensated by reduced losses in patient productivity in the long term.[6] In this regard, discontinuation of bDMARDs in RA patients achieving the treatment target is not warranted.[6] Moreover, in the most aggressive IFX treatment arm, a high rate of bDMARD tapering was achieved.[1] Several studies have reported the outcomes of bDMARD discontinuation in RA patients with sustained clinical remission or LDA.[7,8] In these studies, disease activity flared in some patients who discontinued bDMARDs and it was necessary to restart treatment. It is therefore necessary to determine the efficacy of readministration of bDMARDs in this patient population. Conversely, if readministration of discontinued bDMARDs is shown to be as effective as treatment before discontinuation, bDMARDs could be administered only when flares occur in RA patients who cannot afford the cost of continuous bDMARD treatment.

In clinical practice, patients with RA are reluctant to use bDMARDs because of their high cost, even when administered under the Japanese health insurance system.[9] Patients with RA who cannot afford bDMARDs at the scene of clinics will lose the therapeutic window of opportunity, and joint damage will progress irreversibly.

We conducted a prospective study with historical control patients to examine the sustained efficacy of the bDMARD etanercept (ETN), following its discontinuation when LDA was reached and subsequent readministration in patients with RA. Joint damage was evaluated in these patients at a 2-year follow-up visit.

2. Methods

2.1. Patients

RA patients included in this study were aged 20 years or over with no history of bDMRAD treatment, who met the 1987 American Rheumatism Association classification criteria for RA,[10] and whose disease activity was moderate to high (Disease Activity Score-28 [DAS28]-erythrocyte sedimentation rate [ESR] ≥ 3.2)[11] after receiving methotrexate (MTX) for more than 3 months. Patients with severe joint destruction of the hands and feet were excluded because of the limited ability to obtain radiological measurements for these patients. Patients receiving tacrolimus and/or glucocorticoid at a dose >5 mg/day were also excluded. A total of 32 patients (23 women) were enrolled in this study protocol and provided written informed consent. One patient subsequently discontinued from the study following hospitalization for cerebral infarction before ETN administration. The remaining 31 patients were analyzed as the full analysis set, defined as those who received ETN for at least 4 months.

To compare the extent structural damage among this study population, a series of 16 RA patients treated with full use of ETN was used as a historical control. These patients were consecutively enrolled at our institute from 2008 to 2010 and have been partially described in our previous paper.[12]

Approval for this study was received from the institutional review board or ethics committee at Osaka City University Medical School (date of issue: December 6, 2010, Registration number: #192), and this clinical trial was registered by UMINCTR (http://www.umin.ac.jp/ctr/index-j.htm, UMIN000008164). The institutional review board or ethics committee at each participating institute approved the study protocol, and the study was conducted in accordance with the ethical standards laid down in an appropriate version of the Declaration of Helsinki (as revised in Brazil 2013).

2.2. Study design

This was a prospective, single-arm, multinational, 2-year study which used historical control patients. The primary endpoint of the study was radiographic nonprogression at 2 years. This prospective study was conducted between February 1, 2011 and December 31, 2013 (final follow-up date was October 23, 2014). Patients were administered ETN at 50 mg/week, and treatment was discontinued when LDA (DAS28-ESR < 3.2) was achieved. If disease activity increased over LDA, ETN was restarted at the same dose, with observation every 2 months. This strategy was maintained for 2 years (Fig. 1). If patients were unable to achieve LDA within 6 months of ETN administration, they were considered to be discontinued from the on-demand use study, although data were collected from these patients thereafter (ETN-on group).

2.3. Evaluation

Every 2 months, we evaluated the efficacy of restarting ETN following a flare in disease activity. Radiographs were obtained at baseline and at the 1- and 2-year visits. Radiographic evaluation was performed by 2 of 3 experienced rheumatologists (KI, MT, YS) using van der Heijde’s modified total Sharp score (mTSS; 0–448 points)[13] in a blinded manner. Two physicians who were described in previous sentence masked to the treatment regimens and imaging sequence separately read the digitized radiographic images. Lack of progression was defined as change in mTSS ≤ 0.5 from baseline, and the nonprogression (structural remission) rate was calculated.

2.4. Statistical analysis

Univariate analysis of baseline characteristics was conducted using Fisher exact test for nominal variables, one-way analysis of variance (ANOVA) for continuous variables with normal distribution, and the Kruskal–Wallis test for continuous variables.
with nonnormal distribution. The prognostic factors for discontinuation of ETN more than once were identified with multiple regression analysis, using the variables of gender, age, disease duration, anticitrullinated protein antibody positivity, and use of MTX at baseline. Statistical analysis of structural damage from baseline was determined by Fisher exact test. Logistic regression analysis for structural remission at 1 or 2 years was performed with variables of disease duration, DAS28-ESR, MTX dose, and baseline mTSS. The difference of erosion score and joint narrowing score between on-demand group and historical control group was analyzed by Student t test. All statistical analyses were performed using EZR (version 1.28), a graphical user interface for R (version 3.2.0, The R Foundation for Statistical Computing). More precisely, it is a modified version of R commander (version 2.1-7) designed to provide statistical functions frequently used in biostatistics. All statistical analyses were 2-sided and values of $P < .05$ were considered significant.

### 3. Results

#### 3.1. Baseline characteristics of patients

Of the full analysis set of 31 patients, 13 patients did not discontinue ETN dosage because LDA was never achieved (ETN-on group). Of the remaining 18 patients, 5 maintained LDA throughout the study period after the first instance of ETN stoppage, indicating that successful discontinuation of ETN was achieved (ETN-off group). Among the other 13 patients, ETN was administered repeatedly according to the protocol (on-demand group) (Table 1).

Univariate analysis of the baseline characteristics between the ETN-on group and the other 2 groups revealed that dose of MTX ($P = .042$), use of any csDMARDs ($P = .046$), and body mass index ($P = .007$) were significantly different (Table 1). Multivariate association for the ETN-on group compared to the other 2 groups was performed by logistic regression analysis using 4 factors as independent variables (DAS28-ESR, disease duration, dose of MTX, and ACPA). MTX was significantly correlated with ETN (odds ratio [OR]: 1.29; $P = .017$), that is, RA patients taking a lower dose of MTX were less likely to discontinue ETN at least once (Table 2). Binomial logistic regression analysis for structural remission at 1 or 2 years was conducted among the on-demand group and the historical control group together. The model including age, baseline mTSS, DAS28-ESR, disease duration, and dose of MTX as explanatory variables, and no independent factors were found to exist (Table 3).

#### 3.2. Disease activity in on-demand group

The DAS28-ESR courses for all 13 patients in the on-demand group are shown in Fig. 2A. One solid line indicates one DAS28-ESR course of one patient, which contained at least one set of a peak value $>3.2$ and a trough value $<3.2$. During the observation period, 21 sets of peak and trough values in 13 patients (one set: 7 patients; 2 sets: 4 patients; 3 sets: 2 patients) were recorded in the on-demand group (Fig. 2B). All patients in the on-demand group had achieved LDA at the end of final ON period (Fig. 2B). Mean duration of recurrence from LDA after discontinuation of ETN was $2.7 \pm 1.2$ months (median value 2 months; max 6 months, min 2 months) and mean duration of discontinuation of ETN...
Table 1
Baseline patient characteristics.

|                | ALL (n = 31) | On-demand (n = 13) | ETN-on (n = 13) | ETN-off (n = 5) | P† | Historical control (n = 16) | P† |
|----------------|-------------|-------------------|----------------|---------------|----|---------------------------|----|
| Female/male    | 22/9        | 7/6               | 11/2           | 4/1           | .200a | 13/3                     | .226a |
| Age            | 59.7 ± 14.2 | 60.2 ± 13.8       | 57.4 ± 16.5    | 64.6 ± 9.3    | .638b | 53.3 ± 8.0               | .103b |
| BMI, kg/m²     | 22.0 ± 2.9  | 23.2 ± 2.8        | 20.2 ± 2.1     | 23.4 ± 2.4    | .007bd | 21.7 ± 3.3               | .266bd |
| Disease duration, y | 6.08 [1.71, 19.92] | 5.17 [1.75, 10.50] | 6.75 [1.67, 19.92] | 5.17 [4.53, 24.00] | .658c | 8.90 [4.95, 17.38]       | .273c |
| RF% (APCA%)    | 41.0 ± 25.8 | 77.0 ± 20.6       | 60.0 ± 61.1    | 92.0 ± 100    | .271/196c | 94.9 ± 9.8               | .989/364c |
| DAS28-ESR      | 5.48 ± 1.0  | 5.6 ± 1.1         | 5.5 ± 0.9      | 5.0 ± 0.7     | .442c | 5.2 ± 1.4                | .386c |
| MMP-3, ng/mL   | 173.60 [97.10, 235.70] | 173.80 [92.10, 228.90] | 173.60 [112.30, 492.10] | 113.90 [47.80, 177.30] | .327c | 150.30 [110.80, 221.40]  | .895c |
| HA-DI          | 0.83 ± 0.69 | 0.82 ± 0.60       | 0.89 ± 0.79    | 0.7 ± 0.89    | .866b | 0.91 ± 0.85              | .708b |
| PSL use, n     | 16          | 9 (60%)           | 6 (40%)        | 1 (20%)       | .152a | 9 (56%)                  | .702a |
| CS-DMARDs use, n, (%) | 25      | 13 (100%)         | 8 (62%)        | 4 (80%)       | .046a | 16 (100%)                | 1a |
| MTX, mg/wk     | 9.3         | 9.3 ± 3.9         | 4.5 ± 5.3      | 8.1 ± 4.8     | .042b | 6.4 ± 3.8                | .048b |
| mTSS           | 24.50 [12.88, 94.88] | 16.75 [5.38, 26.25] | 59.75 [14.75, 138.62] | 135.00 [33.00, 233.25] | .199c | 183.00 [112.38, 248.62]  | <.001c |

Table 2
Logistic regression analysis for stop of ETN at least once.

|                | Odds ratio | 95% Confidence interval | P    |
|----------------|------------|-------------------------|------|
| Disease duration | 0.990      | 0.376–2.610             | .984 |
| DAS28-ESR       | 1.020      | 0.907–1.110             | .621 |
| MTX, mg/wk      | 1.200      | 1.050–1.590             | .017 |
| ACPA, U/mL      | 0.991      | 0.962–1.000             | .059 |

ACPA = anticitrullinated peptide antibody, DAS28-ESR = disease activity score-28-erythrocyte sedimentation rate, ETN = etanercept, MTX = methotrexate.

4. Discussion
Recent RA treatment strategies, such as treat-to-target,[1] have emphasized the achievement of at least LDA as soon as possible in order to avoid further joint damage, especially in patients with poor prognosis, to avoid permanent disabilities.[13] For achievement of LDA at an earlier stage of the disease, it is clear that bDMARDs represent the most potent of the DMARDs.[14] In patients with an inadequate response to MTX and/or other csDMARD strategies, with or without glucocorticoid treatment, bDMARDs administered with MTX is the recommended treatment for RA.[5,13] Therefore, it is appropriate that bDMARDs are used in all patients with RA insofar as they can be afforded.

For patients who cannot afford bDMARDs or targeted synthetic DMARDs (tsDMARDs), an alternative treatment target is required which accepts some degree of structural damage, although this contradicts the principles of treat-to-target. Recent reports of triple therapy with MTX plus
sulfasalazine and hydroxychloroquine demonstrated results that were equivalent to combination therapy with bDMARDs.\textsuperscript{[17–20]} However, data on long-term results with triple therapy are required because adherence to this regimen appears to be suboptimal.\textsuperscript{[21]} Biosimilar DMARDs (bsDMARDs) represent another option for these patients, although even bsDMARDs are more expensive than csDMARDs and most patients may discontinue their use. This study shows that the use of ETN at a reduced dose or at spaced intervals may be a realistic option for patients who cannot afford their continuous use.

Emery et al reported sustained efficacy with ETN tapering in patients with early RA. Furthermore, no significant differences in

### Figure 2.

(A) Courses of all individual cases of disease activity score-28–erythrocyte sedimentation rate (DAS28-ESR) in the on-demand group. Thick dotted line indicates the mean DAS28-ESR score. Thin dotted straight transverse line indicates DAS28-ESR = 3.2. (B) Disease activity score-28–erythrocyte sedimentation rate (DAS28-ESR) course for 21 sets in 13 patients in the on-demand group of "start-stop-start-stop," "ON" indicates the time when etanercept was administered, and "OFF" indicates the time when etanercept was discontinued. All 21 sets achieved low disease activity. During the observation period, 1 set of peak and trough levels was observed in 7 patients, 2 sets in 4 patients, and 3 sets in 2 patients.

### Table 4

| Structural remission | 1 y  | 2 y  |
|----------------------|------|------|
|                      | Yes  | No   | P    | Yes  | No   | P    |
| On-demand group (n, %) | 9 (82%) | 2 (18%) | 1 | 6 (50%) | 6 (50%) | .114 |
| Historical control (n, %) | 14 (88%) | 2 (12%) | | 13 (81%) | 3 (19%) |

Statistical analysis was conducted by Fisher exact probability test.
mTSS = modified total Sharp score.
ETN seems a suitable choice for treating disease and should be considered for treatment when patients relapse over at least 2 years. Therefore, on-demand use of ETN may be generally safe and efficacious after long-term continuous therapy and withdrawal was reported.

Readministration of IFX in patients with ankylosing spondylitis showed that episodic IFX retreatment in Crohn's disease was not an indication of losing remission or LDA and radiographic progression on discontinuation of bDMARDs, however, dose reduction of bDMARDs does not increase such risk by the meta-analysis.

In conclusion, the on-demand use of ETN for RA flares reduced the disease activity but did not reduce structural damage in half of the patients over 2 years. However, inhibition of joint damage was achieved in half of the patients at a lower cost, supporting the on-demand use of ETN as an option for the treatment of patients with RA who cannot afford expensive bDMARD or tsDMARD therapy. Therefore, those patients who can afford the cost should continue ETN use, while those who cannot should use ETN on-demand.

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