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BRIEF REPORT

Different expression levels of TNF receptors on the rheumatoid synovial macrophages derived from surgery and a synovectomy as detected by a new flow cytometric analysis

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Abstract TNFα plays a crucial role in the pathogenesis of rheumatoid arthritis. It is very important to examine the expression of the TNF receptors, the ligand of TNFα. In this study, we developed a triple-color flow cytometric analysis using CD45 and CD14 monoclonal antibodies to simply detect the expression of the TNF receptors on the heterogeneous rheumatoid synovial cells. Using this system, we detected a higher population of macrophages and a greater TNF receptor expression on the synovial macrophages derived from a synovectomy in comparison to the findings obtained from knee joint replacement surgery.

Keywords Rheumatoid arthritis · Synovial cell · TNF receptor · Flow cytometry · Synovectomy · Macrophage

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease which is characterized by inflammatory synovitis and bone erosion (Feldmann et al. 1996a; Huber et al. 2006; Muller-Ladner et al. 2007; Schett 2008; Sweeney and Firestein 2004). Although the etiologies of RA have yet to be clearly defined, the persistence of autoreactive cells might lead to cytokine production (i.e., TNFα and IL-6). Recently, TNF blockers have also been used in patients with RA, and many patients have been reported to benefit from these agents (Feldmann and Maini 2001), thus suggesting that TNFα plays an important role in the pathogenesis of RA in patients. TNFα has the ability to bind two distinct TNF receptors, TNFR1 (TNFRSF1A) and TNFR2 (TNFRSF1B) (Baud and Karin 2001; Beyaert et al. 2002; MacEwan 2002; Wallach et al. 1999). The binding of TNFR1 triggers the release of the inhibitory protein silencer of death domains (SODD) and forms a receptor-proximal complex containing the adapter proteins. The engagement of TNF receptors results in the activation of two major transcription factors, nuclear factor κB (NF-κB) and c-Jun. These transcription factors induce the expression of genes that mediate diverse biological processes (Baud and Karin 2001; Beyaert et al. 2002; Chen and Goeddel 2002; MacEwan 2002; Wallach et al. 1999), especially in RA. For this reason, it is very important to examine the expression of TNF receptors on rheumatoid synovial cells.

The rheumatoid synovium contains a variety of cells, including macrophage-like cells (type A), fibroblast-like cells (type B), dendritic-like cells, and infiltrated lymphocytes (Feldmann et al. 1996b). These heterogeneous populations made it difficult to examine the pathogenesis of RA. In this study, we developed a new flow cytometric analysis in the synovial cells regarding the expression of surface molecules on each cell. Using this simple system, we detected a higher population of macrophages and a greater TNF receptor expression on the synovial macrophages derived from a synovectomy in comparison to those from knee joint replacement surgery.

Materials and methods

Cells

Synovial tissue specimens were obtained from patients with RA at the time of orthopedic surgery (knee joint replacement surgery or synovectomy) in the National Ureshino Hospital. Informed consent was obtained from all participating subjects, and the study was conducted in accordance with the human experimental guidelines of our institution. Synovial cells were isolated from the synovial tissues by an enzymatic digestion, as described previously (Yamasaki et al. 2002). Adherent synovial cells of at least four passages were used in this experiment as the cultured synovial cells. Before the analysis of the cultured adherent synovial cells, 0.5 mM EDTA solution with PBS was used to release the cells from the plastic plates. Trypsin–EDTA solution was not used, in order to avoid changes of the expression of surface molecules on the cells.

Monoclonal antibodies (mAb) and flow cytometry

PE-conjugated anti-human CD45, PC5-conjugated anti-human CD14, and PE-conjugated and PC5-conjugated control mAb (IgG1) were purchased from Beckmann Coulter (Hialeah, FL). FITC-conjugated anti-human TNFR1 and anti-human TNFR2 were purchased from R&D (Minneapolis, MN). FITC-conjugated anti-human control mAb (IgG1) were purchased from Beckmann Coulter. The triple-immunofluorescence analysis method has been described in detail elsewhere (Eguchi et al. 1989). The triple-immunofluorescence experiments were analyzed with a flow cytometer (Epics XL; Coulter Electronics, Hialeah, FL).

Results and discussion

We examined the two sources of the rheumatoid synovium which were derived from knee joint replacement surgery and a synovectomy. The disease activity of RA patients who were operated on for knee joint replacement should be low in comparison to that of patients who received a synovectomy, because the knee joint replacement is performed in the majority of RA patients whose knee joints were destroyed after long-time therapy. To elucidate the real status of the rheumatoid synovium, it would be useful to use the cells from the active inflammatory phase in the experiments. This is the reason why synovial cells derived from both knee joint replacement surgery (Fig. 1a) and a synovectomy (Fig. 1b) were used and then the cell population and the expression of TNF receptors were compared between the two sources of synovial cells in this experiment. Figure 1 shows that the main population would be from the macrophage region (CD45+CD14+) in the freshly isolated synovial cells derived from both knee joint replacement surgery and a synovectomy. A higher population of macrophages was detected in the cells from a synovectomy in comparison to those obtained from knee joint replacement surgery (61.9 and 45.8%, respectively). After the isolated synovial cells were cultured for a long time (at least 4 times passages), the percentage of macrophage-like cells was decreased; in contrast, the percentage of fibroblast-like cells was increased in the synovial cells derived from both knee joint replacement surgery and a synovectomy. Regarding the expression of TNF receptors, a small percentage of TNFR1 expressed cells was detected in both the macrophage and fibroblast cell regions in the synovial cells derived from both knee joint replacement surgery and a synovectomy. On the other hand, the TNFR2 expression on the macrophage-like cells was sufficiently detected, whereas no TNFR2 expression was observed on the fibroblast-like cells in the synovial cells derived from both knee joint replacement surgery and a synovectomy (Fig. 1). Interestingly, the expression of both TNFR1 and TNFR2 on the synovial macrophages derived from a synovectomy was higher

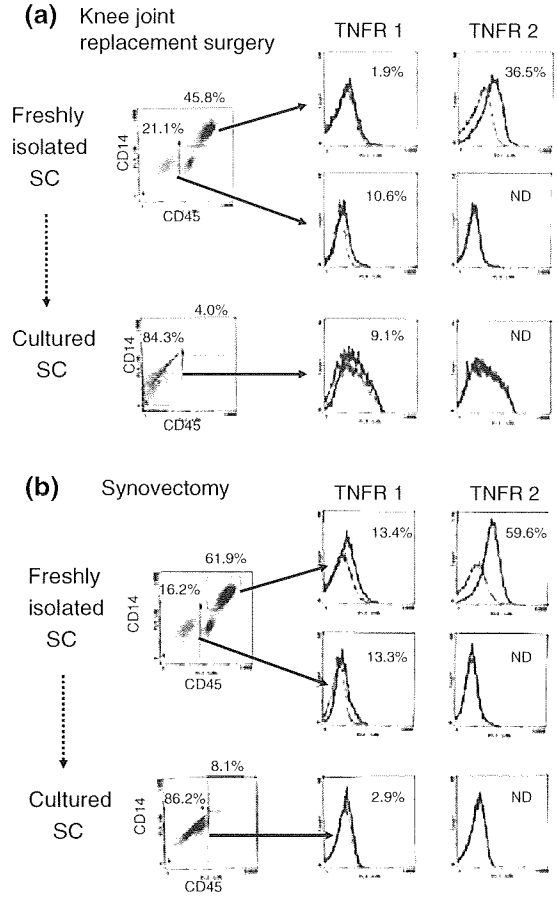

Fig. 1 Altered TNF receptor expression on synovial cells after long-time culture. A triple-color flow cytometric analysis of TNF receptors in the synovial cells derived from knee joint replacement surgery (**a**) and a synovectomy (**b**). Both cells were analyzed for the surface expression of TNF receptors (*TNFR1* and *TNFR2*) on the CD14+CD45+ population or CD14−CD45− population. In the *upper panel* (**a** and **b**), the synovial cells were derived from the freshly isolated cells. In the *lower panel* (**a** and **b**), the synovial cells are derived from the long-time cultured cells. In each histogram, the background fluorescence is recorded with a thin line, and the thick-lined histogram quantifies the expression of the indicated molecules (% = percentage of positive expression of each of the molecules). One of four representative experiments is shown. *SC* synovial cell, *ND* not detected

than that from knee joint replacement surgery (13.4 and 1.9% in TNFR1, 59.6 and 36.5% in TNFR2, respectively), thus suggesting that synovial macrophages from a synovectomy may be more highly activated than those from knee joint replacement surgery, while also reflecting an increased disease activity.

Rheumatoid synovial tissue contains macrophage-like cells (type A), fibroblast-like cells (type B), dendritic-like cells, and infiltrated lymphocytes, demonstrating that these heterogeneous cells would constitute the RA inflammatory synovium (Feldmann et al. 1996b; Karouzakis et al. 2006; Muller-Ladner et al. 2007). We previously reported apoptosis (Kawakami et al. 1999, 2004; Miyashita et al. 2003, 2004; Tamai et al. 2006), cell differentiation (Yamasaki et al. 2004), cell proliferation (Eguchi et al. 1992; Migita et al. 2000, 2001), signal transduction (Yamasaki et al. 2001, 2002), sensitivity to drugs (Migita et al. 2004), and protein expression of the rheumatoid synovial cells (Honda et al. 2001; Tanaka et al. 2004) using the long-time cultured synovial cells derived from the knee joint replacement surgery. As the cell population and the expression of TNF receptors both dramatically changed in the synovial cells derived from both surgery and a synovectomy after long-term cultures (Fig. 1a, b), it would be difficult to evaluate the real function of the rheumatoid synovial cells using such long-term cultured cells. However, we had no chance to use these long-term cultured synovial cells in our previous experiments, because a large number of such cells are needed to perform the assays, and the necessary amount of cells was just not available. If we use this simple flow cytometric method, we can independently evaluate the expression of surface molecules on each cell type derived from the freshly isolated synovial cells, and thus making it possible to elucidate the present status of the RA synovium.

In summary, we developed a simple detection system, which was a triple-color flow cytometric analysis, using CD45 and CD14 monoclonal antibodies on rheumatoid synovial cells. Using this system, we detected a higher population of macrophages and a greater TNF receptor expression on the synovial macrophages derived from a synovectomy in comparison to that obtained during knee joint replacement surgery. This flow cytometric analysis is therefore considered to reflect the real status of the disease using rheumatoid synovial cells, especially those derived from a synovectomy.

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ORIGINAL ARTICLE

A Prediction Rule for Disease Outcome in Patients With Undifferentiated Arthritis Using Magnetic Resonance Imaging of the Wrists and Finger Joints and Serologic Autoantibodies

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Objective. To evaluate whether magnetic resonance imaging (MRI) of the wrists and finger joints and an analysis of serologic autoantibodies are clinically meaningful for the subsequent development of rheumatoid arthritis (RA) in patients with undifferentiated arthritis (UA).

Methods. A total of 129 patients with UA, a disease status formally confirmed by a rheumatologist over a period of at least 1 year, were included. Gadolinium-diethylenetriamine–enhanced MRI of both wrists and finger joints and serologic variables were examined upon admission to our Early Arthritis Clinic at Nagasaki University. After a prospective followup of 1 year, a predictive value for the development of RA was determined for each patient.

Results. The subjects were evaluated for their positive or negative status with respect to 3 objective measures at study entry: anti–cyclic citrullinated peptide (anti-CCP) antibodies and/or IgM-rheumatoid factor, MRI-proven symmetric synovitis, and MRI-proven bone edema and/or bone erosion. The patients who were positive for at least 2 of these measures progressed to RA at 1 year with a 79.7% positive predictive value (PPV), 63.0% negative predictive value, 75.9% specificity, 68.0% sensitivity, and 71.3% accuracy. Furthermore, in 22 UA patients positive for both anti-CCP antibodies and MRI-proven bone edema who were considered to have progressed to RA at 1 year, the PPV was increased to 100%. A close correlation was found between the present rule and that established in the Leiden Early Arthritis Cohort.

Conclusion. MRI-proven early joint damage in conjunction with serologic autoantibodies is efficient in predicting progression from UA to RA. This method can be used to identify patients who would benefit from early treatment with disease-modifying antirheumatic drugs.

INTRODUCTION

Early undifferentiated arthritis (UA) is defined as early arthritis that does not fulfill the classification criteria for a more definitive diagnosis, according to the 1987 American College of Rheumatology (ACR; formerly the American Rheumatism Association) criteria for rheumatoid arthritis (RA) (1–3). The natural disease course of UA is variable; therefore, to minimize under- and overtreatment of patients with UA, a model was recently constructed by the Leiden Early Arthritis Cohort to estimate the likelihood of progression to RA in individual patients (2,3). Their prediction rule consists of 9 clinical variables: sex, age, localization of symptoms, morning stiffness, tender joint count,

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swollen joint count, C-reactive protein (CRP) level, IgM rheumatoid factor (IgM-RF) positivity, and the presence of anti–cyclic citrullinated peptide (anti-CCP) antibodies (2,3). Prediction scores vary from 0 to 14 and correspond to the percent chance of developing RA at 1 year (3). Van der Helm-van Mil et al examined 570 patients with UA and found that, at cutoff levels of ≤6 and ≥8, the negative predictive values (NPVs) and positive predictive values (PPVs) were 91% and 84%, respectively (3), which indicates a score of ≥8 for initiating treatment and a score of ≤6 for withholding treatment.

The above prediction rule indicates that clinical manifestation is still the gold standard in detecting synovitis, which is also mentioned by the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT) (4); however, the expert committee of the European League Against Rheumatism defines the importance of imaging methods such as magnetic resonance imaging (MRI) and ultrasonography as being more sensitive than clinical examination or plain radiography for the detection of early joint damage in early arthritis (4). For instance, plain radiography does not detect synovitis, early bone erosion, or bone edema, whereas MRI is able to do so (5). Given the utility of the detection of early joint damage by MRI, our investigation has focused on how to identify patients with early arthritis likely to progress to RA by not using MRI of the wrists and finger joints and serologic variables (6–8). Our previous reports have shown that MRI-proven symmetric synovitis, MRI-proven bone changes (bone edema or bone erosion), and the presence of serologic autoantibodies (anti-CCP antibodies or IgM-RF) upon admission are predictive factors for early-stage RA (6). However, some of the patients examined in the previous studies already fulfilled international disease criteria for RA or osteoarthritis upon admission (6,7), which was a weak point of our previous prediction rule.

The present study is a reevaluation of our prediction rule in patients with UA. Additionally, we examined correlations with a predictive role such as that reported by the Leiden Early Arthritis Cohort.

PATIENTS AND METHODS

Patients. The Early Arthritis Clinic opened in 2001 as a part of the Unit of Translational Medicine, the Department of Immunology and Rheumatology, and the Graduate School of Biomedical Sciences at Nagasaki University. Patients were referred from an area in the western part of Japan, Nagasaki Prefecture, which has ~450,000 inhabitants. From this clinic, 129 patients with UA were included in the present study; their disease status was formally confirmed by a rheumatologist for at least 1 year. We have examined MRI results of both wrists and finger joints for all of the subjects; therefore, all of the 129 patients with UA expressed rheumatic manifestations of the wrists and finger joints at study entry. The characterization of UA upon admission was determined as previously reported (3), i.e., as arthritis that could not be classified according to ACR criteria within 2 weeks after being included in the study, when laboratory and radiographic results were available. At a prospective followup of 1 year, 75 patients were found to have progressed to RA based on the 1987 ACR criteria for RA (1).

Baseline clinical manifestations and variables included sex, age, localization of arthritis, morning stiffness score measured on a 100-mm visual analog scale, the number of tender joints, the number of swollen joints, the CRP level (measured by latex turbidimetric immunosorbent assay; Daiichi Pure Chemicals, Fukuoka, Japan), IgM-RF positivity (measured by latex-enhanced immunonephelometric assay with a cutoff value of 14 IU/ml; Dade Behring, Marburg, Germany), positive status for anti-CCP antibodies (measured by enzyme-linked immunosorbent assay [ELISA] with a cutoff value of 4.5 units/ml; DIASTAT Anti-CCP; Axis-Shield, Dundee, UK), matrix metalloproteinase 3 (measured by ELISA with cutoff values of 59.7 ng/ml for women and 121.0 ng/ml for men; Daiichi Pure Chemicals) (9), and MRI of both wrists and finger joints, as previously described (6–8). All variables were examined on the same day, as previously reported (6–8). Each patient provided a signed consent form to participate in the study, which was approved by the Institutional Review Board of Nagasaki University.

MRI of the wrists and finger joints. MRI of both wrists and finger joints were acquired using a 1.5T system (Sigma; General Electric Medical Systems, Milwaukee, WI) with an extremity coil. Coronal T1-weighted spin-echo (repetition time [TR] 450, echo time [TE] 13) and STIR (TR 3,000, TE 12, T1 160) images were also acquired. The images were evaluated for bone edema, bone erosion, and synovitis in 15 sites in each finger and wrist, including the distal radioulnar joint, the radiocarpal joint, the midcarpal joint, the first carpometacarpal joint, the second through fifth carpometacarpal joints (together), the first through fifth metacarpophalangeal joints, and the first through fifth proximal interphalangeal joints separately (a total of 30 sites in both hands), as we recently reported (6–8). The presence of synovitis, bone edema, and bone erosion was evaluated by 2 experienced radiologists (MU, ST) as described by Lassere et al (10) and Conaghan et al (11), and decisions were reached by consensus. The evaluation of MRI features has been established by several groups (10–13); however, it is a complex task. Therefore, as we previously reported (6–8), we simply determined the presence or absence of synovitis, bone edema, and bone erosion on MRI after the intravenous injection of 0.1 mmoles/kg of gadolinium-diethylenetriamine (Magnevist, Schering, Germany). Our method is qualitative rather than quantitative; however, it is sensitive enough to identify early joint damage in patients with early-stage RA (6–8).

Assessment of disease status at 1 year and statistical analysis. Our previous reports have shown the preferential expression of MRI-proven symmetric synovitis, MRI-proven bone edema, MRI-proven bone erosion, IgM-RF, and anti-CCP antibodies in patients with early-stage RA (6–8). Logistic regression analysis of the previous study identified subjects with positive values for 2 or 3 of the 3 objective measures (anti-CCP antibodies and/or IgM-RF, MRI-proven symmetric synovitis, and MRI-proven bone

Table 1. Baseline characteristics of 129 patients with undifferentiated arthritis*

	RA progression (n = 75)	No RA progression (n = 54)	P†
Age, median (range) years	53 (25–80)	52 (16–79)	NS
Sex, male:female (% female)	17:58 (77.3)	12:42 (77.8)	NS
Duration of symptoms at baseline, median (range) months	3 (0.5–15)	3 (0.5–24)	NS
Morning stiffness, median (range) minutes	60 (0–960)	15 (0–960)	< 0.0005
Tender joint count, median (range)	7 (0–39)	4.5 (0–27)	< 0.05
Swollen joint count, median (range)	3 (0–26)	0 (0–24)	< 0.0001
DAS28 tender joint count, median (range)	6 (0–28)	4 (0–24)	< 0.005
DAS28 swollen joint count, median (range)	3 (0–23)	0 (0–22)	< 0.0001
HAQ score, mean ± SD	7.3 ± 4.3	4.8 ± 3.8	< 0.005
Patients' pain on a 100-mm VAS, mean ± SD	52.6 ± 27.1	52.4 ± 32.0	NS
Patients' global on a 100-mm VAS, mean ± SD	52.5 ± 25.4	56.4 ± 29.5	NS
1987 ACR criteria for RA‡			
Morning stiffness for 1 hour	41 (54.7)	15 (27.8)	< 0.005
Arthritis in ≥3 joints	42 (56.0)	10 (18.5)	< 0.00001
Arthritis of the wrists and finger joints	56 (74.7)	22 (40.7)	0.0001
Symmetric arthritis	41 (54.7)	11 (20.4)	< 0.0001
IgM-RF positivity	39 (52.0)	16 (29.6)	< 0.05
HLA–DRB1*0405 allele carriership	27 (36.0)	13 (24.1)	NS
DAS28-CRP, mean ± SD	4.31 ± 1.22	3.46 ± 1.33	< 0.0001
Serologic variables			
Anti-CCP antibody positivity	43 (57.3)	4 (7.4)	< 0.0001
IgM-RF and/or anti-CCP antibody positivity	50 (66.7)	18 (33.3)	< 0.0005
MMP-3 positivity	27 (36.0)	8 (14.8)	< 0.01
MMP-3 level, median (range) ng/ml	50.2 (0–1,250)	34.8 (10.66–419.6)	< 0.005
CRP positivity	51 (68.0)	16 (29.6)	< 0.0001
CRP level, median (range) mg/dl	0.50 (0.01–18.4)	0.10 (0–8.36)	< 0.0001
MRI features			
Synovitis positivity	68 (90.7)	30 (55.6)	< 0.0001
Symmetric synovitis positivity	56 (74.7)	22 (40.7)	< 0.005
Bone edema positivity	31 (41.3)	5 (9.3)	< 0.0001
Bone erosion positivity	22 (29.3)	5 (9.3)	< 0.0001
Bone edema and/or erosion positivity	36 (48.0)	9 (16.7)	< 0.0001

* Values are the number (percentage) unless otherwise indicated. RA = rheumatoid arthritis; NS = no significant difference; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire; VAS = visual analog scale; ACR = American College of Rheumatology; IgM-RF = IgM rheumatoid factor; CRP = C-reactive protein; anti-CCP = anti–cyclic citrullinated peptide; MMP-3 = matrix metalloproteinase 3; MRI = magnetic resonance imaging.
† Indicates the difference between RA progression and no RA progression.
‡ We did not refer to the duration of the components in the 1987 ACR criteria for RA: morning stiffness for 1 hour, arthritis in ≥3 joints, arthritis of the wrists and finger joints, and symmetric synovitis.

edema and/or bone erosion); the patients were classified as having early-stage RA with 82.5% sensitivity and 84.8% specificity (6). However, our previous study is somewhat inaccurate because some of the subjects were already classified as having early-stage RA or rheumatic diseases other than RA upon admission (6). Therefore, in the present study, all of the selected subjects were classified as having UA upon admission, having been evaluated by the same objective measures in comparison with the prediction rule by the Leiden Early Arthritis Cohort (3). For all tests (chi-square test, Mann-Whitney U test, and Spearman's rank correlation), P values less than 0.05 were considered significant.

RESULTS

Evaluation of the Leiden Early Arthritis Cohort prediction rule in 129 UA patients. We collected the demographic clinical manifestations, serologic data, and MRI features of 129 patients with UA upon admission (Table 1). As expected, these arthritis conditions were condensed in UA that progressed to RA, as compared with UA that did not progress to RA. Although the choice of therapies for the patients was based on the decision of each physician, the difference between clinical manifestations at baseline may reflect on the therapies within the first year. Therefore, the percentage of patients receiving disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids was much higher in 75 patients with UA that progressed to RA than in 54 patients with UA that did not progress to RA. In regard to DMARDs, 63 (84.0%) of 75 patients with UA that progressed to RA were treated with DMARDs, including 39 patients with sulfasalazine, 13 patients with methotrexate, 2 patients with infliximab, and 1 patient with adalimumab, whereas only 3 patients (5.6%) received DMARDs among 54 patients with UA that did not progress to RA ($P < 0.0001$). In regard to glucocorticoids, 45 (60.8%) of 75 patients with UA that progressed to RA were

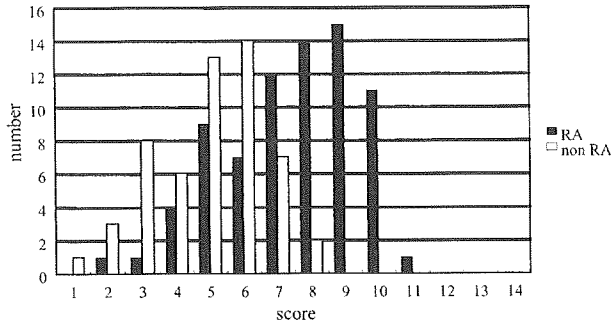

Figure 1. Scoring of 129 patients with undifferentiated arthritis by the Leiden Early Arthritis Cohort prediction rule; 75 had progressed to rheumatoid arthritis (RA) at 1 year. The distribution of the scores at baseline is shown, calculated according to the Leiden Early Arthritis Cohort prediction rule. Scores were rounded to the nearest number encoding in 0.5 or 0.0 (i.e., scores ≤0.5 are in category 0, scores >0.5 to 1.5 are in category 1, etc.), as described previously (3). RA = progression to RA group (n = 75); non RA = no progression to RA group (n = 54).

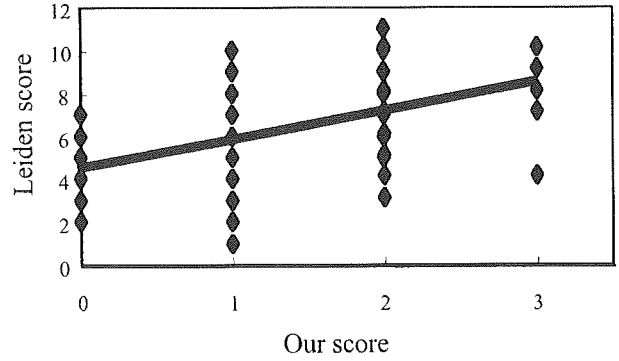

Figure 2. A positive correlation between the Leiden Early Arthritis Cohort prediction score and our prediction score. The statistical association was calculated by Spearman's rank correlation and a strong correlation was found between the 2 scores (R = 0.635, $P < 0.0001$).

treated with glucocorticoids, whereas 10 patients (18.5%) received glucocorticoids among 54 patients with UA that did not progress to RA ($P < 0.0001$). The diagnoses of 54 patients with UA that did not progress to RA at 1 year include Sjögren's syndrome (n = 11), osteoarthritis (n = 9), chronic hepatitis (n = 6), scleroderma (n = 3), palindromic rheumatism (n = 3), systemic lupus erythematosus (n = 2), fibromyalgia syndrome (n = 2), adult-onset Still's disease (n = 1), myofasciitis of unknown etiology (n = 1), polymyalgia rheumatica (n = 1), remitting seronegative symmetrical synovitis with pitting edema (n = 1), pseudogout (n = 1), and UA (n = 13). The Leiden Early Arthritis Cohort prediction scores were also calculated. Figure 1 shows the distribution of prediction scores, with a mean high score in patients with UA that progressed to RA of 8 versus 5 in patients with UA that did not progress to RA ($P < 0.0001$). According to cutoff levels of ≤6 and ≥8 in the Leiden Early Arthritis Cohort prediction rule, the NPV and PPV were 67.2% and 95.3%, respectively, in the present study population.

Evaluation of the prediction rule by serologic variables and MRI in comparison with the Leiden Early Arthritis Cohort prediction score. We evaluated the prediction rule by serologic variables and MRI in patients with UA, according to our previous report (6–8) as described above. The statistics demonstrate that the PPV was 79.7%, the NPV was 63.0%, the specificity was 75.9%, the sensitivity was 68.0%, and the accuracy was 71.3%. With respect to UA patients whose Leiden Early Arthritis Cohort prediction score was ≥8 (n = 43; PPV of 95.3% among the 41 of these 43 patients who progressed to RA by the Leiden Early Arthritis Cohort prediction score), our prediction rule was able to classify the progression to RA equally well (38 [88.4%] of 43 patients, not significantly different versus the Leiden Early Arthritis Cohort prediction score). In addition, with respect to UA patients whose Leiden Early Arthritis Cohort prediction score was ≤6 (n = 67; NPV of 67.2% among the 45 patients who did not progress to RA by the Leiden Early Arthritis Cohort prediction score), the present prediction rule predicted that 52 of 67 patients would not progress to RA (77.6%; not significantly equal to the Leiden Early Arthritis Cohort prediction rule). Fifteen of 67 patients whose Leiden Early Arthritis Cohort prediction score was ≤6 at baseline were classified as having RA by our score, and in fact, 7 patients progressed to RA at 1 year (PPV in this population is 46.7%). Accordingly, a positive correlation between the Leiden Early Arthritis Cohort prediction score and our score was clearly determined (R = 0.635, $P < 0.0001$) (Figure 2). Furthermore, the 3 critical objective characteristics were preferentially found among UA patients whose Leiden Early Arthritis Cohort prediction score was ≥8 as compared with those whose score was ≤6 (Table 2). Anti-CCP antibodies and MRI-proven bone edema were the most specifically distributed in UA patients with a score of ≥8 (Table 2).

Table 2. Distribution of MRI-proven symmetric synovitis, MRI-proven bone edema, anti-CCP antibodies, and IgM-RF in 129 patients with UA according to the Leiden Early Arthritis Cohort prediction score*

	Leiden Early Arthritis score		
	Score ≤6 (n = 67)	Score ≥8 (n = 43)	*P*
Symmetric synovitis	44.8	81.4	0.0001
Bone edema	10.4	48.8	< 0.0001
Bone erosion	13.4	30.2	0.032
Anti-CCP antibodies	6.0	86.0	< 0.0001
IgM-RF	26.9	67.4	< 0.0001
CRP level	38.8	69.8	0.0015
MMP-3	16.4	37.2	0.013
Progression to RA	32.8	95.3	< 0.0001

* Values are the percentage. Compared with patients with undifferentiated arthritis (UA) who scored ≤6, MRI-proven symmetric synovitis, MRI-proven bone edema, anti-CCP antibodies, and IgM-RF were densely distributed in the UA patients who scored ≥8. See Table 1 for definitions.

Table 3. Qualification of each variable at baseline for the prediction of progression to rheumatoid arthritis from undifferentiated arthritis*

	Sensitivity, %	Specificity, %	OR	*P*	95% CI	PPV, %	NPV, %	LR positive	LR negative	Accuracy, %
Serologic variables										
IgM-RF	52.0	70.4	2.57	< 0.05	1.53–4.34	70.9	51.4	1.76	0.682	59.7
Anti-CCP antibodies	57.3	92.6	16.8†	< 0.0001†	7.63–36.99	91.5†	61.0	7.74	0.461	72.1
MMP-3	36.0	85.2	3.23	< 0.01	1.73–6.03	77.1	48.9	2.43	0.751	56.6
MRI findings										
Symmetric synovitis	74.7	59.3	4.07	< 0.005	2.52–7.30	71.8	62.7	1.84	0.427	68.2
Bone edema	41.3	90.7	6.90†	< 0.0001†	3.34–14.29	86.1†	52.7	4.44	0.647	62.0
Bone erosion	29.3	90.7	4.07	< 0.0001	1.94–8.52	81.5	48.0	3.18	0.779	55.0

* OR = odds ratio; 95% CI = 95% confidence interval; PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; see Table 1 for additional definitions.
† Most significant in serologic variables or MRI findings.

Procedure for the improvement of PPV for the prediction of RA development by our objective measures. The present data showed a 79.7% PPV for the prediction of RA development using our objective measures, which is not sufficient evidence to recommend that physicians start administering DMARDs if the patients do not yet fulfill the established classification criteria. According to *P* values and odds ratios of independent predictive variables for the development of RA, anti-CCP antibodies as a serologic variable and bone edema on MRI were found to be the most specific (Table 3). Therefore, if UA patients tested positive for anti-CCP antibodies and showed MRI-proven bone edema, they will progress to RA within 1 year; the PPV in such cases was 100% (Table 4). In the case of the score in Table 4, we examined MRI-proven bone edema of the symptomatic hand instead of both hands. As shown in Table 4, the PPV in such cases was still 100%, whereas the sensitivity of detection was low as compared with both hands (16 patients by the symptomatic hand versus 22 patients by both hands, 27.3% reduction by the symptomatic hand).

DISCUSSION

In clinical practice, patients presenting with early arthritis frequently have an undifferentiated disease that may progress to polyarthritis by fulfilling the ACR criteria for RA, or they may have a more benign disease course. The ACR criteria have been criticized for their low discriminative ability in patients presenting with recent-onset arthritis (14–16). Therefore, a new set of criteria that applies to early UA and that identifies patients with UA who will progress to RA is needed, since a recent study strongly suggests that treatment is effective in the early phase of arthritis, before the disease is established (4).

To our knowledge, the present study is the first validation report of Japanese patients with UA using the Leiden Early Arthritis Cohort prediction rule. The Leiden Early Arthritis Cohort prediction rule is clinically useful, especially to identify patients who will progress to RA, i.e., those whose prediction score is ≥8. However, a difference was found in the low NPV of the Leiden score in our study population as compared with the original report (91% NPV in the original report from The Netherlands) (3). This could be due to the fact that the present study population may have included more RA patients with low disease activity whose disease developed from UA compared with the original study population in The Netherlands. In addition, the rate of progression to RA in this cohort is high as compared with previous observations, including the Leiden Early Arthritis Cohort (3,17). The Leiden Early Arthritis Cohort has identified that the presence of arthritis

Table 4. An achievement of 100% PPV for the development of RA from UA by a combination of anti-CCP antibodies and MRI-proven bone edema*

No. patients	Variables at baseline: Anti-CCP antibodies	Variables at baseline: Bone edema by both hands	Variables at baseline: Bone edema by the symptomatic hand	RA progression (n = 75)	No RA progression (n = 54)
22	Positive	Positive		22 (100)	0 (0.0)
25	Positive	Negative		21 (84.0)	4 (16.0)
14	Negative	Positive		9 (64.3)	5 (35.7)
68	Negative	Negative		23 (33.8)	45 (66.2)
16	Positive		Positive	16 (100)	0 (0.0)
31	Positive		Negative	27 (87.1)	4 (12.9)
10	Negative		Positive	5 (50.0)	5 (50.0)
72	Negative		Negative	27 (37.5)	45 (62.5)

* Values are the number (percentage). PPV = positive predictive value; RA = rheumatoid arthritis; UA = undifferentiated arthritis; anti-CCP = anti–cyclic citrullinated peptide; MRI = magnetic resonance imaging.

in the wrists and finger joints, as well as in the upper extremities at study entry, is an advantage in the progression of RA (3). All of the subjects in the present study expressed rheumatic manifestations of the wrists and finger joints; therefore, they could already be selected as being biased to the progression of RA. This discrepancy may cause a difference in the prediction efficacy of the Leiden Early Arthritis Cohort prediction rule toward the 2 cohort populations. A prospective clinical analysis of the present study population, including a radiographic joint damage study, is necessary to answer this question.

There is a significant difference between our score and that established by the Leiden Early Arthritis Cohort, with respect to not only the prediction rule but also to the selection of the variables. The Leiden Early Arthritis Cohort adopted a cutoff value of ≥8 for the PPV and ≤6 for the NPV for the prediction, whereas our score can draw a threshold of only one line of prediction. The Leiden Early Arthritis Cohort variables stress clinical manifestations; however, our scoring system gives weight only to serologic autoantibodies and early joint damage as verified by MRI. The NPV of the 2 prediction rules was similar (63.0% versus 67.2%), although the PPV was superior in the Leiden score (79.7% versus 95.3%). Nevertheless, our prediction rule identified 52 patients of 65 predicted upon admission, whereas the Leiden score identified only 41 patients of 43 predicted. In an attempt to improve the PPV, we demonstrated that the combination of anti-CCP antibodies with bone edema gave a 100% PPV in 22 patients (Table 4). Considering the significant correlation between the 2 rules, our prediction rule is considered to be equally valuable to predict the development of RA in patients with UA.

The ESCISIT states that clinical examination is still the gold standard in detecting synovial inflammation; however, the expert committee is aware of the importance of MRI in greater sensitivity for detection (4). In the case of the patients who progressed to RA that were identified by our prediction rule rather than by the Leiden score, MRI helped identify patients with UA who were not able to be identified by clinical manifestation. The result that our rule can predict the progression of RA whose Leiden Early Arthritis Cohort prediction score was ≤6 at baseline may reflect this notion. Our present data give clear evidence of MRI that is sensitive as well as clinically valuable for patients with early arthritis. Based on a combination of serologic anti-CCP antibodies, we suggest that a UA patient whose score is ≥2 should receive DMARDs early, especially if they both show MRI-proven bone edema and are anti-CCP positive. We also tried to simplify the method by using MRI of the symptomatic hand instead of both hands, in the case of seeking MRI-proven bone edema. In this case, detection sensitivity decreased by 27.3%, whereas the PPV was still 100%. This would show practical advantages for clinical use if a single-hand MRI is as good as both hands; however, additional studies by other groups are necessary.

It remains to be determined whether the present rule is also effective in predicting radiographic joint destruction. It is likely to be effective, since bone change in MRI as well as serologic autoantibodies are predictors for subsequent radiographic progression (10,11,16,17). The present prediction rule revealed that patients with early-stage RA with both MRI-proven bone edema and anti-CCP antibodies upon admission progressed with a high frequency to erosive disease (Tamai M et al: unpublished observations). However, a prospective analysis of the present study remains to be carried out in order to precisely answer these questions.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Eguchi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Tamai, Kawakami, Uetani, Aoyagi, Eguchi.

Acquisition of data. Tamai, Kawakami, Uetani, Takao, Arima, Iwamoto, Fujikawa, Aramaki, Kawashiri, Ichinose, Kamachi, Nakamura, Origuchi, Ida, Eguchi.

Analysis and interpretation of data. Tamai, Kawakami, Aoyagi.

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ORIGINAL ARTICLE

Prediction of DAS28-ESR remission at 6 months by baseline variables in patients with rheumatoid arthritis treated with etanercept in Japanese population

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Abstract We tried to determine which baseline variables are responsible for remission induction at 6 months in unselected rheumatoid arthritis (RA) patients of Japanese population treated with etanercept. One hundred forty-one patients with RA who were administered etanercept were registered. Thirty-four patients were started on etanercept monotherapy, 60 patients on cotherapy with methotrexate (MTX) (MTX cotherapy), and 47 patients on cotherapy with other non-MTX nonbiologic disease-modifying antirheumatic drugs (DMARDs) (non-MTX cotherapy). None of the patients were treated with both MTX and non-MTX nonbiologic DMARDs at entry. Outcome was set as achievement of disease activity score 28 (DAS28)-ESR remission at 6 months. We examined association of gender, DAS at baseline, MTX cotherapy at baseline, non-MTX cotherapy at baseline, and prednisolone use at baseline with achievement of remission at 6 months by logistic regression analysis. All subjects were classified as having high ($N = 109$) or moderate disease activity ($N = 32$) at entry. One hundred twenty out of 141 patients (85.1%) continued treatment with etanercept at 6 months. Continuation rate was statistically higher in MTX cotherapy (93.3%) compared with etanercept monotherapy

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(73.5%), and tended to be higher than with non-MTX cotherapy (85.1%). Logistic regression analysis identified that MTX cotherapy at entry and moderate disease activity at entry were independent variables for remission induction at 6 months. Accordingly, DAS28-ESR at 6 months was significantly lower with MTX cotherapy as compared with etanercept monotherapy or non-MTX cotherapy. To a lesser extent, DAS28-ESR with non-MTX cotherapy at 6 months was lower than with etanercept monotherapy. In this study of unselected patients, use of MTX and moderate disease activity at entry were associated with higher likelihood of response to etanercept. Non-MTX nonbiologic DMARDs may be an alternative in RA patients administrated etanercept who are intolerant to MTX.

Keywords Etanercept · Rheumatoid arthritis · MTX · Non-MTX nonbiologic DMARDs · DAS28-ESR

Abbreviations

ACR	American College of Rheumatology
DAS	Disease activity score
DMARDs	Disease-modifying antirheumatic drugs
MTX	Methotrexate
RA	Rheumatoid arthritis
TNF-α	Tumor necrosis factor-α

Introduction

Randomized controlled trials of anti-tumor necrosis factor-α (anti-TNF-α) therapies including etanercept in rheumatoid arthritis (RA) have shown etanercept to be superior to placebo and to methotrexate (MTX) monotherapy in patients with active RA [1, 2]. The trial of etanercept and methotrexate with radiografic patient outcomes (TEMPO) study compared etanercept with MTX, starting each as new monotherapy or both as combination therapy, and found the combination to be superior to either drug alone [3]. However, the majority of patients in clinical practice who will receive etanercept will already have received nonbiologic disease-modifying antirheumatic drugs (DMARDs) including MTX yet have ongoing disease activity. In addition, the dosage as well as kinds of nonbiologic DMARDs used in clinical practice of RA in Japan are different from in Western countries, thus evidence for clinical practice effectiveness of etanercept should be established in Japanese patients.

In this study, we investigated whether baseline variables at treatment initiation are associated with clinical response to treatment with etanercept, and show that MTX cotherapy as well as moderate disease activity are predictive for remission induction at 6 months.

Patients and methods

Patients

Patients were recruited from the Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, Sasebo Chuo Hospital, Kurume University School of Medicine, Gotokai Hospital, The Japanese Red Cross Nagasaki Atomic Bomb Hospital, Nagasaki Citizen Hospital, Isahaya General Hospital, NHO Ureshino Medical Center, and NHO Nagasaki Medical Center. Written form of informed consent approved by the above hospitals was obtained from each patient. Patients who received with both MTX and non-MTX nonbiologic DMARDs at entry were omitted from this observational study. At entry, 152 patients were recruited; however, at evaluation 11 patients were excluded due to combined use of MTX and non-MTX nonbiologic DMARDs. Thus, data of 141 RA patients, who received etanercept for 6 months, were collected. All of the patients fulfilled the 1987 criteria of the ACR for RA [4]. Disease activity was evaluated by disease activity score 28 (DAS28)-ESR and all of the patients had high ($N = 109$) or moderate disease activity ($N = 32$) at entry. Thirty-four patients entered the study as etanercept monotherapy, 60 patients as cotherapy with methotrexate (MTX) (MTX cotherapy), and 47 patients as cotherapy with other non-MTX nonbiologic DMARDs (non-MTX cotherapy). Non-MTX nonbiologic DMARDs included leflunomide ($N = 8$), tacrolimus ($N = 5$), salazosulufapyridine ($N = 8$), mizoribine ($N = 10$), bucillamine ($N = 11$), D-penicillamine ($N = 1$), tiopronin ($N = 10$), cyclosporine A ($N = 3$), and actarit ($N = 2$). Although the MTX cotherapy group did not receive other nonbiologic DMARDs at entry, some of the non-MTX cotherapy patients received two (tacrolimus + salazosulufapyridine, one patient; leflunomide + mizoribine, one patient; salazosulufapyridine + mizoribine, two patients; bucillamine + tiopronin, four patients; mizoribine + actarit, one patients) or three kinds (bucillamine + tiopronin + D-penicillamine, one patient; bucillamine + tiopronin + cyclosporine A, one patient) of nonbiologic DMARDs.

Statistical analysis

Distribution of baseline variables was examined by Mann–Whitney U test, Kruskal–Wallis test, and χ^2 test. Logistic regression analysis was performed to investigate relationships between baseline variables and clinical efficacy at 6 months. Clinical efficacy was set in the present study as achievement of DAS28-ESR remission (less than 2.6) at 6 months. Etanercept continuation rate at 6 months was also examined. DAS28-ESR at 6 months was judged by the

last observation carried forward (LOCF) approach. Baseline variables were gender, DAS28-ESR at baseline [high disease activity ($\geq$5.1) versus moderate disease activity (3.2 $\leq$ DAS28-CRP $<$ 5.1)], MTX at initiation (MTX cotherapy), cotherapy with non-MTX nonbiologic DMARDs (non-MTX cotherapy) at initiation, and prednisolone at initiation. Prednisolone >5 mg/day at initiation was also examined for logistic regression analysis. *P* value less than 0.05 is considered to be significant.

Results

Baseline variables of 141 patients with RA treated with etanercept for 6 months and drug survival at 6 months

Table 1 summarizes the data. Most of the patients had established disease, with mean disease duration of 10.4 years at baseline. None of the patients received biologic DMARDs (infliximab, adalimumab, tocilizumab) other than etanercept during the 6 months. All 141 patients expressed high ($N = 109$) or moderate disease activity ($N = 32$) at baseline (Table 1). Baseline variables, including age, gender, duration of disease, MTX use at initiation, and prednisolone use at initiation were not different between patients with high and moderate disease activity (Table 1). At the end of 6 months follow-up period, 120 patients continued etanercept. The continuation rate at 6 months was 93.3% (56 out of 60 patients) in MTX cotherapy, 85.1% (40 out of 47 patients) in non-MTX cotherapy and, 73.5% (25 out of 34 patients) in etanercept monotherapy ($P = 0.004$ for MTX cotherapy versus etanercept monotherapy, $P = 0.09$ for MTX cotherapy versus non-MTX cotherapy). The reasons for discontinuation, judged by each physician, were the following. In the etanercept monotherapy group, one patient discontinued due to lack of efficacy, skin eruption, angina pectoris or perforation of sigmoid colon; six patients discontinued due to respiratory tract infection; and one patient complicated with two adverse events at discontinuation. In non-MTX cotherapy group, one patient discontinued due to lack of efficacy, itching of skin, compression fracture of the spine or sepsis; and three patients discontinued due to respiratory tract infection. In MTX cotherapy group, one patient discontinued due to elevation of liver enzymes or respiratory tract infection; and two patients discontinued due to skin eruption.

MTX cotherapy and moderate disease activity at initiation are independent predictors for DAS28-ESR remission at 6 months

Table 2 shows the data for the logistic regression analysis. As shown in Table 2A, MTX cotherapy and moderate disease activity at baseline were independent predictors of remission induction at 6 months. Similar results were obtained if the dosage of prednisolone at initiation was limited to >5 mg/day (Table 2B). Other variables (gender, non-MTX cotherapy, and prednisolone at initiation) did not reach statistical significance. Accordingly, baseline variables among MTX cotherapy, non-MTX cotherapy, and etanercept monotherapy were similar except for slight difference of age at initiation (Table 3). We examined the change of DAS28-ESR during 6 months. DAS28-ESR at initiation did not differ among the three treatment groups; however, as expected, DAS28-ESR at 6 months was significantly low with MTX cotherapy as compared with

Table 1 Characteristics of RA patients at entry

	Baseline characteristics	Baseline DAS28-ESR		
	All patients	High group	Moderate group	*P* value
No. of patients	$N = 141$	$N = 109$	$N = 32$	–
Age, years, mean ± SD	56.8 ± 13.9	56.0 ± 14.3	59.5 ± 11.9	0.22
Gender (male/female)	32/109	24/85	8/24	0.73*
Duration of disease, years	10.4 ± 8.9	9.9 ± 8.7	12.0 ± 9.4	0.47
DAS28-ESR, mean ± SD	5.85 ± 1.06	6.28 ± 0.73	4.39 ± 0.55	<0.01
High (>5.1)	$N = 109$ (77.3%)	$N = 109$	–	–
Moderate (3.2–5.1)	$N = 32$ (22.7%)	–	$N = 32$	–
MTX use at baseline (yes/no)	60/81	49/60	11/21	0.20*
PSL use at baseline	$N = 124$ (87.9%)	$N = 99$ (90.8%)	$N = 25$ (78.1%)	0.06*
PSL >5 mg at baseline	$N = 72$ (51.1%)	$N = 57$ (52.3%)	$N = 15$ (46.9%)	0.37*

Baseline characteristics, including age, gender, duration of disease at baseline, MTX use at baseline, and prednisolone use at baseline, were not different between DAS28-ESR high ($N = 109$) and DAS28-ESR moderate patients ($N = 32$). The distribution is characterized by Mann–Whitney *U* test or * χ^2 test as described in the text

Table 2 Logistic regression analysis to estimate remission induction by etanercept

Baseline variables	Comparison	Odds ratio	95% CI	*P* value
(A) Variables: gender, MTX at initiation, nonbiologic DMARDs other than MTX at initiation, prednisolone at initiation, DAS28-ESR				
Gender	Male/female	0.76	0.22–2.60	0.66
MTX	Yes/no	4.65	1.13–19.09	0.03
DMARDs other than MTX	Yes/no	1.47	0.31–7.03	0.63
Prednisolone	Yes/no	0.56	0.16–2.01	0.38
Disease activity(DAS28-ESR)	Moderate/high	4.08	1.43–11.55	0.008
(B) Variables: gender, MTX at initiation, nonbiologic DMARDs other than MTX at initiation, prednisolone > 5 mg/day at initiation, DAS28-ESR				
Gender	Male/female	0.70	0.20–2.43	0.57
MTX	Yes/no	4.68	1.14–19.16	0.03
DMARDs other than MTX	Yes/no	1.47	0.31–7.05	0.63
Prednisolone >5 mg/day	Yes/no	0.46	0.17–1.24	0.13
Disease activity(DAS28-ESR)	Moderate/high	4.27	1.52–12.00	0.006

MTX use at initiation and moderate disease activity at baseline are predictive for remission induction

Table 3 Comparison of baseline characteristics among MTX cotherapy, non-MTX nonbiologic DMARDs cotherapy, and etanercept monotherapy groups

	MTX cotherapy	Non-MTX nonbiologic DMARDs cotherapy	Etanercept monotherapy	*P* value
No. of patients	$N = 60$	$N = 47$	$N = 34$	–
Age, years, mean ± SD	54.4 ± 13.2	59.5 ± 12.3	57.1 ± 16.7	0.046
Gender (male/female)	12/48	9/38	11/23	0.30
Duration of disease, years	9.3 ± 7.9	11.4 ± 9.0	10.9 ± 10.4	0.69
DAS28-ESR, mean ± SD	5.97 ± 1.01	5.87 ± 1.04	5.58 ± 1.13	0.45
High (>5.1)	$N = 49$ (81.7%)	$N = 37$ (78.7%)	$N = 23$ (67.6%)	0.29
Moderate (3.2–5.1)	$N = 11$ (18.3%)	$N = 10$ (21.3%)	$N = 11$ (32.4%)	0.29
PSL use	$N = 52$ (86.7%)	$N = 42$ (89.4%)	$N = 30$ (88.2%)	0.91
PSL >5 mg	$N = 30$ (50.0%)	$N = 25$ (53.2%)	$N = 17$ (50.0%)	0.94

Baseline characteristics, including age, gender, duration of disease at baseline, DAS28-ESR at baseline, distribution of DAS28-ESR, and prednisolone use at initiation were not different among MTX cotherapy, non-MTX nonbiologic DMARDs cotherapy, and etanercept monotherapy groups except for slight difference of age at entry. The distribution is characterized by Kruskal–Wallis test as described in the text

etanercept monotherapy ($P < 0.0001$) and non-MTX cotherapy ($P = 0.009$) (Fig. 1). In addition, DAS28-ESR at 6 months of non-MTX cotherapy was statistically low as compared with etanercept monotherapy ($P = 0.04$) (Fig. 1). Rate of DAS28-ESR remission at 6 months was 26.7% (16 out of 60) with MTX cotherapy, 12.8% (6 out of 47) with non-MTX cotherapy, and 8.9% (3 out of 34) with etanercept monotherapy, being significantly higher with MTX cotherapy ($P = 0.03$, MTX cotherapy versus etanercept monotherapy).

Discussion

The results of this study support the benefit of combined use of etanercept with MTX, which performed better than etanercept alone or etanercept in combination with non-MTX nonbiologic DMARDs. This is reasonable, but provides important information for clinical practice in Japan since the MTX dosage is quite low and non-MTX nonbiologic DMARDs are different than in Western countries. The trend for non-MTX cotherapy to be better than etanercept monotherapy is also similar to the observational study of Western countries described by Hyrich et al. [5] and Kristensen et al. [6]. All RA patients administered etanercept will not be tolerant to nonbiologic DMARDs. However, physicians need to recognize that MTX and, to a lesser extent, non-MTX nonbiologic DMARDs improve the efficacy of etanercept.

Male gender was selected as a predictor of remission induction in the TEMPO study, whereas this was not found in the present study. MTX dosage is clearly different

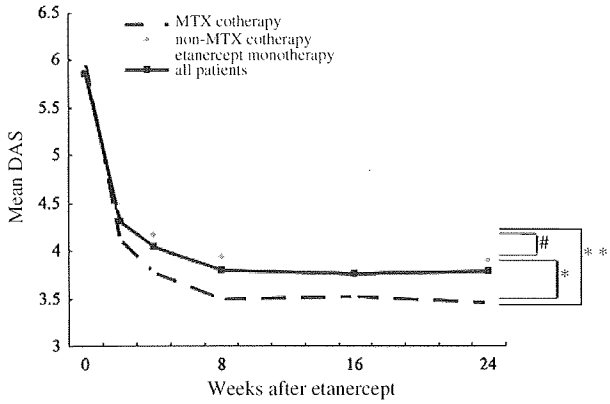

Fig. 1 Change of DAS28-ESR in patients with RA treated by MTX cotherapy, non-MTX cotherapy, and etanercept monotherapy during 6 months. DAS28-ESR after entry was calculated by LOCF approach. DAS28-ESR at entry were not different among MTX cotherapy, non-MTX cotherapy, and etanercept monotherapy. At 6 months, DAS28-ESR was significantly decreased in MTX cotherapy as compared with etanercept monotherapy and non-MTX cotherapy. In addition, DAS28-ESR at 6 months of non-MTX cotherapy was statistically low as compared with etanercept monotherapy. $^{**}P < 0.0001$: MTX cotherapy versus etanercept monotherapy $^{*}P = 0.009$: MTX cotherapy versus non-MTX cotherapy. $^{\#}P = 0.04$: non-MTX cotherapy versus etanercept monotherapy. Differences were examined by Mann–Whitney *U* test

between the two groups and the TEMPO study does not include RA patients treated with non-MTX nonbiologic DMARDs, which may explain the different results.

Systemic administration of low-dose glucocorticoids is effective in relieving short-term signs and symptoms in patients with RA, although its role in disease outcome remains obscure [7]. This study does not show efficacy of low-dose glucocorticoids in patients with RA treated by etanercept. Preferably, treatment of RA by glucocorticoids should be temporary because of the risk of side-effects and lack of an add-on effect to etanercept.

The TEMPO study identified patients with lower disease activity at initiation to be more likely to reach remission. Accordingly, moderate disease activity at entry was predictive of remission induction as compared with patients with high disease activity. Similar results were also obtained in Japanese RA patients treated with infliximab [8], suggesting that this demography may be a common indicator for good therapeutic response to DMARDs in patients with RA.

There are limitations to comparing treatment outcomes based on observational data, since the decision to treat patients is not random, but is highly dependent on a number of factors, such as disease severity, patient choice and compliance, and comorbidities. Similarly, the decision to stop therapy because of inefficacy or adverse events in this real-world study was at the direction of the rheumatologist and was not subject to strict protocol. However, we still found a significant difference between combined use of etanercept plus nonbiologic DMARDs, especially for MTX as compared with etanercept monotherapy, and between high and moderate disease activity at initiation for the achievement of good therapeutic efficacy. Our data provide clinical benefit for etanercept use in clinical practice.

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Conflict of interest statement None.

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CASE REPORT

Rheumatoid vasculitis of crural muscles confirmed by muscle biopsy in the absence of inflammatory myopathy: histologic and MRI study

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Abstract A 60-year-old man who had been diagnosed as rheumatoid arthritis admitted to our hospital by dysesthesia on his legs with edema. Nerve conduction velocity test led to diagnosis of mononeuritis multiplex. Magnetic resonance imaging (MRI) of lower legs showed high intensity in slow tau inversion recovery. Typical vasculitis with neutrophil-dominant cell infiltration was observed by muscle biopsy without inflammatory myopathy or fascitis. Diagnosis was made by rheumatoid vasculitis found in crural muscles. Intravenous cyclophosphamide with oral tacrolimus effectively improved dysesthesia with reduction of inflammatory response.

Keywords Rheumatoid vasculitis · Magnetic resonance imaging · Muscle biopsy · Cyclophosphamide

Abbreviations

IVCY	Intravenous cyclophosphamide
MRI	Magnetic resonance imaging
NCV	Nerve conduction velocity
PAN	Polyarteritis nodosa
RA	Rheumatoid arthritis
STIR	Slow tau inversion recovery

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that affects multiple organs as well as synovial joints [1]. Extra-articular manifestations of RA contain cardiopulmonary abnormalities, hematological or neurological manifestations [2]. Although rheumatoid vasculitis represents various organ involvements such as pleuritis, ocular manifestations or neuropathies based on systemic vasculitis, the relationship between imaging abnormality and pathological characteristics of rheumatoid vasculitis is rarely reported. In the present case, we show typical vasculitis, comparing to magnetic resonance imaging findings.

Case report

A 60-year-old man had been diagnosed as RA according to a criteria determined by American college of rheumatology [3]. Although he was treated with salazosulfapyridine or methotrexate, he recently began to feel dysesthesia on his bilateral legs with edema. Since local heat and swelling of lower legs also appeared, oral prednisolone was increased

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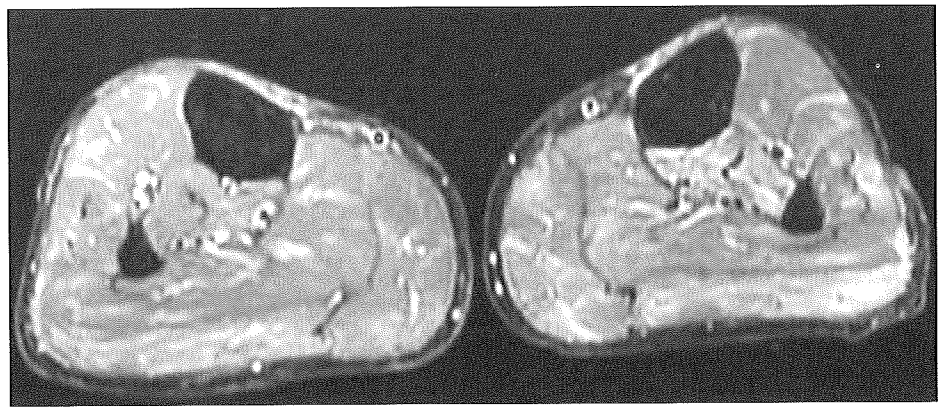

Fig. 1 Magnetic resonance imaging of the left lower leg. Slow tau inversion recovery (STIR) image shows patchy high intensity of gastrocnemius muscle or tibialis posterior muscle in the patient

to 20 mg/dl with discontinuation of disease modifying antirheumatic drugs. In February 2009, he was admitted to our hospital due to these persistent symptoms. He felt dysesthesia, especially on his left legs with edema and erythema, although no skin ulcer was observed.

Laboratory findings showed a hemoglobin level of 14.0 g/dl, total leukocyte count of 14,400/mm^3 and a platelet count of 37.2×10^4/mm^3. Although transaminases, renal function, creatinine kinase and aldolase levels were within normal limit, C-reactive protein was elevated to 6.99 mg/dl with accelerated erythrocyte sediment rate (99.2 mm/h, normal range <15). Although serum IgG and IgA were within normal limits, both rheumatoid factor (76.7 IU/ml, normal range <14) and anti-cyclic citrullinated peptide antibody (>100 U/ml, normal range <4.5) were positive without anti-SS-A or anti-SS-B antibody. On admission, he showed moderate disease activity of 3.82 points by disease activity score (DAS) 28-ESR. Antineutrophil cytoplasm antibodies (ANCAs), cryoglobulins, antiphospholipid antibodies, hepatitis B antigen, and angiotensin converting enzyme were negative. Radiographically, X-ray of his both hands represented bone erosion and joints narrowing as Steinblocker stage III. Since he had sensory disturbance of bilateral lower extremities, nerve conduction velocity (NCV) test was performed. The results showed a decrement of amplitude on the left leg with diagnosis of mononeuritis multiplex. Magnetic resonance imaging (MRI) of lower legs showed high intensity in slow tau inversion recovery (STIR) (Fig. 1). Because myositis, myofascitis or edema was suspected from the MRI findings, muscle biopsy of the lesion was performed, resulting in typical vasculitis with neutrophil-dominant cell infiltration (Fig. 2) without inflammatory myopathy, fascitis or sarcoidosis. Diagnosis was made by rheumatoid vasculitis found in the crural muscles. Since inflammatory myopathy was not found in the muscle biopsy specimens, STIR high lesion was considered to be edematous change induced by vasculitis. This may be consistent with clinical manifestation of absent muscle weakness. Intravenous cyclophosphamide

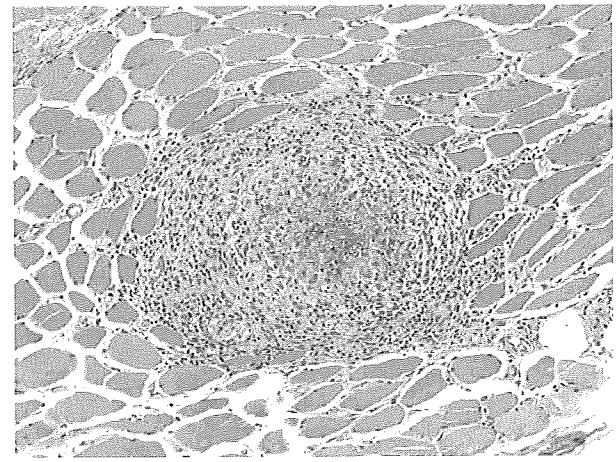

Fig. 2 Typical vasculitis in the biopsy specimen. Around small vessel in muscle of the left lower leg, typical vasculitis with neutrophil-dominant cell infiltration was accompanied by leukocytoclastic vasculitis. Neither myositis nor myofascitis was observed. (original magnification, ×100)

(IVCY) was monthly introduced twice with oral 3 mg of tacrolimus. These therapies were effective, showing obvious improvement of dysesthesia with reduction of CRP from 6.99 to 1.88 mg/dl; he was discharged.

Discussion

A variety of extra-articular manifestations were found in RA. Although Turesson et al. [4] reviewed extra-articular manifestations in RA, peripheral neuropathy is one of these clinical entities. Gorson [5] showed that vasculitis was seen in so-called vasculitis syndromes such as polyarteritis nodosa (PAN) or secondary process of other connective tissue diseases including RA. From the diagnostic approach of rheumatic vasculitis, NCV study or subsequent muscle biopsy seem to be crucial to confirm vasculitis. Especially, biopsy specimen directly gives us available information to detect vasculitis.

In our case, positive MRI findings ended up with neutrophil-infiltration dominant vasculitis. Gallien et al. [6] previously demonstrated positive MRI findings in T2 weighed and STIR in PAN patients. Although vasculitis was restricted in limbs in their cases, the positive MRI findings were considered to be increased muscle fluid content. As they showed, the MRI findings are observed in both edema and myopathies. Since myopathy was absent in our case, edema-like change as a result of vasculitis might exist.

In summary, we show positive MRI findings and subsequent pathological confirmation of typical vasculitis without myositis or fascitis. Since our case responded to IVCY therapy based on existence of vasculitis, MRI is beneficial before performing muscle biopsy in case of rheumatoid vasculitis with peripheral neuropathy.

Conflict of interest statement The authors declare no conflict of interest.

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