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Original Article

A study on characteristics of rheumatoid arthritis patients achieving remission in depression with 6 months of bDMARDs treatment

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Abstract

Objective: To investigate the relationship between baseline factors and depression remission after a 6-month biological disease-modifying antirheumatic drugs (bDMARDs) treatment in rheumatoid arthritis (RA) patients.

Methods: The study was conducted in 152 RA patients treated with bDMARDs. The following patient's characteristics were studied: gender, age, disease duration, baseline prednisolone dosage, and serum matrix metalloproteinase3 (MMP3) levels. For assessment, we used the simple disease activity index (SDAI) for RA disease activity, Health Assessment Questionnaire Disability Index (HAQ-DI) for activities of daily living (ADL), Short Form-36 for nonspecific health-related quality of life (QOL), and Hamilton Depression Rating Scale (HAM-D) scores for the depression status. Depressed remission was clarified using HAM-D ≤7 after 6 months of treatment. The patients were divided into two groups according to the presence or absence of depression, and a retrospective study was conducted.

Results: Based on binominal logistic analyses, RA patients' with depression remission (n=124) compared to those without depression remission (n=28) had a younger age (p=0.0045, odd ratio: 0.94, 95% confidence interval [CI]:0.8-0.98), female sex (p=0.021, odd ratio:0.21, 95% CI:0.054-0.79), and lower HAM-D scores (p=0.0073, odd ratio:0.85, 95% CI:0.76-0.96)

Conclusion: It was proposed that RA patients who are females, younger in age, and have lower depressed scores at baseline can achieve a depression remission status with the bDMARDs treatment.

Keywords: Depression, rheumatoid arthritis, bDMARD, remission, predictor

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Introduction

The recommendations of the treatment of rheumatoid arthritis (RA) and the usage of methotrexate (MTX) as an anchor agent have been well established (1). In combination, MTX with biological disease-modifying antirheumatic drugs (bDMARDs), has contributed to an increased amount of patients who have achieved clinical remission. As a result of this increase in the rate of clinical remission, the number of patients achieving structural and functional remission has also increased (2-5). Complete remission in a patient is defined as the achievement of clinical, functional, and structural remission (6).

Approximately 15% of RA patients also worry about depression, with an odds ratio of 1.42 (95% confidence interval [CI]:1.3-1.5) compared with healthy people (7, 8). A previous study has reported that biological agents can improve the depressed state associated with RA (9). Age, race, and health assessment questionnaire (HAQ) scores have been reported to affect the depression of RA patients (8, 10). Although prior studies have been cross-sectional, there were no reports that analyzed factors that led to depression remission.

In this study, we investigated the relationship between various baseline factors and depression remission after a 6-month biologic agent treatment.

Methods

A retrospective study was accomplished in patients treated in the centers of Division of Rheumatology Department of Medicine Showa University Hospital, Showa University Koto-Toyosu Hospital, and Showa

University Northern Yokohama Hospital. RA patients who initiated bDMARDs treatment from January 1, 2007, to March 31, 2016 were registered in the database of All Showa University in Rheumatoid Arthritis (ASHURA). Among 384 patients treated with bDMARDs in the ASHURA database, 152 patients' measured Hamilton Depression Rating Scale (HAM-D) was inserted in this study. The selection of bDMARDs, primary physician, and patient were consulted. The choice between subcutaneous injection and intravenous drip, primary physician, and the patient was also consulted.

The following items were evaluated at baseline (i.e., before the bDMARDs treatment) and 6 months after treatment initiation: background items, including sex, age, body mass index (BMI), experience of bDMARDs usage (i.e., either bio-naïve or bio-switch), disease duration, prednisolone dosage, and MTX dosage. Blood examinations included an assessment of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and matrix metalloproteinase3 (MMP3). The disease activity of RA was evaluated using the Simplified Disease Activity Index (SDAI) (11). The activities of daily living (ADL) were evaluated using the HAQ disability index (HAQ-DI), and the nonspecific health-related quality of life (QOL) was evaluated using the Short-Form 36 (SF-36) (12-14). The patient's depression level was evaluated using HAM-D (15). On the occasion of enforcement of HAM-D, YM captured the interview training from SK, and YM conducted HAM-D interview for all patients. SK checked all the results of the HAM-D score and used a 17-item HAM-D score evaluation.

The HAM-D score ≥8 was defined as depression. As a primary outcome index, a HAM-D score £7 was defined as remission in depression. To establish the relationship between baseline factors and depression outcomes, the baseline values of each item were analyzed based on the presence or absence of depression remission. The study exclusion criteria included discontinuation of biologic treatment according to primary or secondary response failure or adverse effects; additional oral treatment using conventional synthetic DMARDs (csDMARDs), corticosteroids, or non-steroidal anti-inflammatory drugs (NSAIDs); complications, such as infection; and the likelihood of continuing the study because of various situations, such as hospital transfer, patient withdrawal from the study, incomplete data, or other circumstances that the primary physician considered inappropriate for the study. We did not study the complications with the Sjogren's syndrome, systemic lupus erythematosus, and mixed connective tissue disease affecting depression.

Table 1. Univariable analysis of the demographics and baseline characteristics of 152 RA patients

		Remission in depression (Group A)	No remission in depression (Group B)	p
	n	124	28	
	Age (years)	53 (42-65)	63 (57-73)	0.000*
	Sex (female), n (%)	107 (86.3)	19 (67.9)	0.039**
	Body mass index (kg/m^2)	21.0 (19.8-23.8)	21.1 (19.6-24.3)	0.69*
	Bio-naive (%)	69.4	75.0	0.37**
	Disease duration (years)	3.9 (1.3-9.4)	4.1 (2.0-10.8)	0.66*
	Prednisolone dosage (mg/d)	2.5 (0-5.0)	4.0 (0.75-5.0)	0.095*
	MTX dosage (mg/w)	8 (6-10)	8 (4-10)	0.14*
bDMARDs	Infliximab	46	9	0.126**
	Etanercept	16	2	
	Adalimumab	16	7	
	Golimumab	8	2	
	Certolizumab Pegol	8	0	
	Tocilizumab	23	3	
	Abatacept	7	5	
	ESR (mm/H)	29 (14-53)	39 (20-60)	0.27*
	CRP (mg/dL)	1.2 (0.33-3.6)	2.3 (0.40-5.3)	0.33*
	MMP3 (ng/mL)	147.0 (74.1-312.0)	225.0 (164.2-311.1)	0.021*
	SDAI	21.5 (13.4-30.0)	26.9 (23.1-34.8)	0.058*
	HAQ-DI	0.375 (0-0.75)	0.8125 (0.25-1.375)	0.015*
HAM-D score	before treatment	4 (2-7)	9 (5.75-12.5)	0.001*
	HAM-D ≥8 (%)	28 (22.6)	17 (60.7)	0.000**
	after treatment	2 (0-4)	10 (8-12.25)	0.001*
	HAM-D ≥8 (%)	0 (0)	28 (100)	0.000**
SF-36	PCS	30.1 (18.9-39.1)	22.2 (11.5-32.9)	0.26*
	MCS	50.8 (43.9-56.2)	46.4 (42.1-53.0)	0.26*
	RCS	46.5 (33.7-57.1)	34.6(20.7-43.3)	0.009*

MTX: methotrexate; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MMP3: matrix metalloproteinase 3; SDAI: simplified disease activity index; HAQ-DI: health assessment questionnaire disability index; HAM-D: Hamilton Depression Rating Scale; SF-36: short form-36; PCS: physical component summary score; MCS: mental component summary score; RCS: role/social component summary score

*analysis using Mann-Whitney U test

**analysis using chi-squared test for independence

All the statistical analyses were performed using the univariate and multivariate analyses in the JMP13 software program (SAS Institute Inc.; Cary, NC, USA). We obtained written informed consent from all patients who registered in the study. The study received approval from the Bio-Ethics Committee of the Department of Medicine, Showa University School of Medicine (No. 1435).

Results

In total, 152 patients registered in the study. No patient received additional oral treatment with steroids or NSAIDs during the treatment period. For the background parameters of the study subjects, there were 124 patients with depression remission (Group A) and 28 without depression remission (Group B; Table 1). Based on univariate analyses, Group A had a significantly younger age (p≤0.001), female

Table 2. Prognostic factor identified using multivariate analysis showing a significant association with depression remission

	Remission in depression	No remission in depression	Odd ratio (95% CI)	p
Age	53 (42-65)	63 (57-73)	0.94 (0.89-0.98)	0.0045
Sex (male), n (%)	107 (86.3)	19 (67.9)	0.21 (0.054-0.79)	0.021
HAM-D score	4 (2-7)	9 (5.75-12.5)	0.85 (0.76-0.96)	0.0073

HAM-D: Hamilton Depression Rating Scale; CI; confidence interval

sex (p=0.039), lower serum MMP3 (p=0.021), lower HAQ-DI (p=0.015), lower HAM-D score (p=0.018), and a higher Role/Social component summary score (RCS) in the SF-36 (p=0.009) compared to Group B. Because the HAQ score and physical component summary score (PCS) in SF-36 mildly correlated (r=0.470, 95% CI:-0.563, -0.365), PCS was excluded from the variables of the multivariate analysis. Similarly, HAM-D and mental component summary score (MCS) in SF-36 mildly correlated (r=0.350, 95% CI:-0.457, -0.234), MCS was excluded from the variables of the multivariate analysis. The multivariate analyses findings were as follows: younger age (p=0.0045, odds ratio:0.94, 95% CI:0.89-0.98), female sex (p=0.021, odds ratio: 0.21, 95% CI: 0.054-0.79), and lower HAM-D score (p=0.0073, odds ratio: 0.85, 95% CI:0.76-0.96) (Table 2).

Discussion

Our study determined that RA patients who are females, younger in age, and have lower HAM-D scores at baseline may achieve depression remission with a biologic agent treatment.

In the present study, the women had a higher fatigue score, pain score, and RA disease activity (16-18). Although women had a lower ADL score, clinical and functional remission were reported, and there were no significant differences between women and men for radiographic findings and CRP (19-21). In older men and women, women had more depressive symptoms (22). Previous studies have reported that women were more depressed, and in this study, men were less likely to have a depressed state. The reason is unknown.

Depression is commonly seen in young people at a high frequency in Europe and the United States. However, the pattern of age-specific frequency differs from country to country. Recent surveys in Japan have reported that depression is high in young as well as middle-aged individuals (23, 24). In a previous report, the incidence of complication of depression is reported as about 15%, whereas it was higher in this study. The reasons are as follows: 1) the RA disease activity was high in patients, 2) HAM-D score is not a tool for diagnosing depression, and 3) the target age of patients was high. However, the present study seems to indicate a higher age resulting in no improvement in depression. A low depressive state before treatment meets the expectation that it leads to depression remission.

Several limitations of this study should be acknowledged. First, we did not perform a radiographic evaluation of the joints. In RA patients, fatigue had no significant association with pain, disease activity, and disability or bone erosions but was associated with depression and anxiety (25). Therefore, it is unlikely that depression is directly linked to a radiographic evaluation. Second, the study design was not prospective but retrospective. Third, the history of major depression was not examined. Fourth, we used HAM-D score for the diagnosis of depression instead of the psychiatrist diagnosis. Finally, no socioeconomic factors were included in our analysis.

In conclusion, our study demonstrated that RA patients who are females, younger in age, and have lower HAM-D scores at baseline may achieve depression remission with bDMARDs treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from the Bio-Ethics Committee of the Showa University School of Medicine (Decision No: 1435).

Informed Consent: Written informed consent was obtained from all the patients who participated in this study.

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