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Original Article

Effect of Drug Adherence on Treatment Outcome in Rheumatoid Arthritis

Yoon-Jeong Oh[1], Bumhee Park[2,3], Ki Won Moon[1]

[1]Division of Rheumatology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, [2]Department of Biomedical Informatics, Ajou University School of Medicine, [3]Office of Biostatistics, Ajou Research Institute for Innovative Medicine, Ajou University Medical Center, Suwon, Korea

Objective. The present study aimed to evaluate the effect of drug adherence on treatment outcome in Korean patients with rheumatoid arthritis (RA). **Methods.** A total of 2,694 RA patients who had complete data from annual follow-ups over three years in the Korean Observational Study Network for Arthritis were included in this study. Patients were divided into adherent and non-adherent groups according to data for drug adherence over three years. The European League against Rheumatism response and rate of disease flare were compared between two groups over three years. We also compared continuous variables representing treatment outcomes between the two groups. **Results.** After propensity score matching using a ratio of 1:3, patients were allocated into non-adherent (n = 522) and adherent (n = 1,447) groups. The rate of non-response was higher in the non-adherent group over three years; however, there were no significant differences between continuous variables related to treatment outcome between the two groups. To evaluate the difference according to disease duration, patients were classified into early and late RA based on 48-month disease duration. In patients with early RA, the adherent group had lower patient's global health visual analog scale and lower disease activity 28 scores at three years compared with the non-adherence group. In patients with late RA, the non-adherent group had a higher rate of disease flare. **Conclusion.** The adherent group tended to show lower disease activity, especially in early RA, whereas the non-adherence group was associated with non-response and higher risk of disease flare. **(J Rheum Dis 2019;26:264-272)**

Key Words. Rheumatoid arthritis, Treatment adherence, Treatment outcome

INTRODUCTION

Drug adherence is important for positive health outcomes, particularly in chronic diseases such as rheumatoid arthritis (RA). There have been many studies to date in RA into the relationship between drug adherence and treatment outcomes. A meta-analysis by Li et al. [1] found that disease activity was significantly lower in adherent patients as compared with non-adherent patients. In Japan, the risk of disease flare was shown to be significantly lower in highly adherent patients with early RA [2]. However, drug adherence was not as high in patients with RA in a real clinical practice setting. The drug adherence rate in RA patients varied between 49.5% and 98.5% depending on the definition and methods used to measure adherence [3]. In Korea, there have been some studies to date into drug adherence in RA. While these have mostly investigated the prevalence and possible causes of non-adherence, there have been no studies to date into the effects of drug adherence on treatment outcome of RA. Therefore, the present study aimed to evaluate the effect of drug adherence on clinical response and rate of disease flare in Korean patients with RA.

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Corresponding to : Ki Won Moon http://orcid.org/0000-0002-4182-8328
Division of Rheumatology, Department of Internal Medicine, Kangwon National University School of Medicine, 1 Gangwondaehak-gil, Chuncheon 24341, Korea. E-mail : kiwonmoon@kangwon.ac.kr

MATERIALS AND METHODS

Study population

Data were collected from the Korean Observational Study Network for Arthritis (KORONA) database [4]. Patients aged ≥18 years who satisfied the 1987 American College of Rheumatology (ACR) classification criteria for RA were recruited between July 2009 and March 2013 from 23 rheumatology centers. Demographic data, clinical features, laboratory data, radiological findings, health-related outcomes, treatment modality, resource utilization, and health behavior were collected from patients in this cohort. A total of 5,376 patients were enrolled at baseline and participated in annual follow-ups. After three years, at the fourth follow-up, 2,783 patients remained in the cohort. Among these patients, we analyzed data from 2,694 patients who had participated in all four follow-ups and completed all the drug adherence questionnaires. The number of participants at each follow-up and the details of the study population are shown in Figure 1.

Measurement of drug adherence

Self-reported questionnaires were used to evaluate drug adherence. The question "How many days did you fail to take medication in the preceding 60 days?" had a six-item scale response: 1, taken daily; 2, failed 1∼5 days; 3, failed 6∼15 days; 4, failed 16∼30 days; 5, failed 30 days or more; and 6, not prescribed any medication. The questionnaire was completed at each annual visit, and data were collected four times over three years. We added the total number of days each patient failed to take medication for 240 days over 3 years and classified this as 1, taken daily; 2, failed 1∼20 days; 3, failed 21∼60 days; 4, failed 61∼120 days; and 5, failed ≥120 days. We defined the adherent group as patients who failed to take medication for <20 days, and the non-adherent group as patients who failed to take medication for >20 days during the 240 days of investigating drug adherence over 3 years.

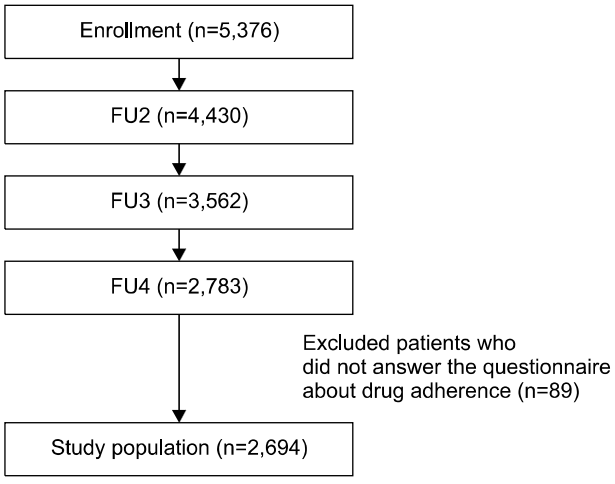

Figure 1. Patient selection flow chart. FU2: second follow-up, FU3: third follow-up, FU4: fourth follow-up.

Data collection and evaluation of disease activity

Clinical characteristics included age, sex, body mass index (BMI), disease duration, number of 1987 ACR classification criteria fulfilled, morning stiffness, current smoker, side effects, income per month, level of education, rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (ACPA), use of RA medication including: methotrexate (MTX); non-steroidal anti-inflammatory drugs (NSAIDs); glucocorticoids; use of biologics; physician's visual analog scale (VAS) score; patient's pain VAS score; patient's global health VAS score; disease activity score 28 (DAS28); EuroQol-5D (EQ-5D); health assessment questionnaire (HAQ); erythrocyte sedimentation rate (ESR); and C-reactive protein (CRP) levels.

Statistical analyses

The primary outcome of the present study was the rate of European League against Rheumatism (EULAR) response and disease flare. EULAR response was calculated using DAS28-ESR between enrollment and the fourth follow-up [5]. Disease flare was defined according to previously validated criteria: increase in DAS28-ESR >1.2 compared with baseline; or increase in DAS28-ESR >0.6 compared with baseline and concurrent DAS28-ESR > 3.2 [6]. Disease flare was evaluated at each follow-up, and defined as any flare that occurred during the follow-up period over three years. The secondary outcome was continuous variables related to treatment outcomes (physician's VAS score, patient's global health VAS score, DAS28-ESR, EQ-5D, HAQ, ESR, and CRP) at each follow-up. Propensity score matching (PSM) was applied to control for differences in baseline characteristics between the two groups (1:3 ratio; 1 for non-adherent and 3 for adherent group). The covariates used for PSM were age, sex, BMI, disease duration, number of 1987 ACR classification criteria fulfilled, morning stiffness, side effects, income, education, RF, ACPA, MTX, NSAIDs, glucocorticoids, biologics, physician's VAS score, patient's global health VAS score, DAS28-ESR, EQ-5D, HAQ, ESR, and

CRP. The expectation–maximization algorithm was used to input missing values. Chi-square test and student's t-test were used for binary and continuous covariates, respectively. All analyses were performed using IBM SPSS software version 24.0 (IBM, Armonk, NY, USA). Results with p-values <0.05 were considered statistically significant.

Ethics statement

The study was approved by the Institutional Review Board of the Kangwon National University Hospital (KNUH-2018-09-009). All participants provided informed consent and the protocol was approved by the Institutional Review Board.

RESULTS

Among 2,694 patients, 2,161 were allocated to the adherent group, and 533 were allocated to the non-adherent group. The baseline characteristics of the two groups before and after PSM are shown in Table 1. The adherent group was older and had longer disease duration, fewer

Table 1. Baseline characteristics between adherent and non-adherent groups before and after PSM using a ratio of 1:3

Variable	Before PSM			After PSM		
	Adherent (n = 2,161)	Non-adherent (n = 533)	p-value	Adherent (n = 1,447)	Non-adherent (n = 522)	p-value
Age (yr)	54.14 ± 10.98	50.26 ± 12.01	<0.01*	51.57 ± 10.85	50.49 ± 11.94	0.07
Sex, female	1,852 (85.7)	473 (88.7)	0.06	1,265 (87.4)	462 (88.5)	0.54
BMI	22.77 ± 3.22	22.56 ± 3.07	0.19	22.62 ± 3.21	22.56 ± 3.06	0.71
Disease duration (mo)	84.59 ± 64.97	74.91 ± 57.41	<0.01*	77.11 ± 61.07	75.46 ± 57.54	0.59
ACR criteria number						
<4	101 (4.7)	22 (4.1)	0.36	63 (4.4)	21 (4.0)	0.74
≥4	2,060 (95.3)	511 (95.9)		1,384 (95.6)	501 (96.0)	
Current smoker	146 (6.8)	38 (7.1)	0.26	97 (6.7)	37 (7.1)	0.96
Side effects	715 (33.1)	229 (43.0)	<0.01*	556 (38.4)	220 (42.1)	0.18
Income (USD/mo)						
<2,000	1,430 (66.5)	297 (55.8)	<0.01*	876 (60.5)	296 (56.7)	0.09
2,000~4,990	574 (26.7)	184 (34.6)		466 (32.2)	180 (34.5)	
≥5,000	145 (6.7)	51 (9.6)		105 (7.3)	46 (8.8)	
Education						
Middle school or less	950 (44.2)	1,201 (55.8)	<0.01*	541 (37.4)	173 (33.1)	0.09
High school or more	174 (32.6)	359 (67.4)		906 (62.6)	349 (66.9)	
Rheumatoid factor	1,493 (69.1)	386 (72.4)	0.14	1,042 (72.0)	375 (71.8)	0.96
ACPA	1,486 (68.8)	352 (66.0)	0.23	976 (67.4)	344 (65.9)	0.52
Medication						
MTX	1,867 (86.4)	460 (86.3)	0.94	1,250 (86.4)	450 (86.2)	0.94
NSAID	1,795 (83.1)	444 (83.3)	0.95	1,203 (83.1)	434 (83.1)	1.00
Steroid	1,805 (83.5)	444 (83.3)	0.90	1,191 (82.3)	433 (83.0)	0.79
Biologics	170 (7.9)	26 (4.9)	<0.05*	77 (5.3)	26 (5.0)	0.82
Physician's VAS score	24.42 ± 18.17	22.05 ± 16.39	<0.01*	22.55 ± 17.09	22.11 ± 16.45	0.61
Patient's GH VAS score	37.86 ± 25.64	37.65 ± 25.23	0.86	37.06 ± 25.61	37.44 ± 25.23	0.77
DAS28-ESR	3.67 ± 1.30	3.57 ± 1.30	<0.05*	3.58 ± 1.28	3.57 ± 1.30	0.85
EQ5D	0.69 ± 0.23	0.72 ± 0.23	<0.05*	0.71 ± 0.22	0.72 ± 0.23	0.67
HAQ	0.66 ± 0.62	0.56 ± 0.58	<0.01*	0.58 ± 0.56	0.56 ± 0.58	0.53
ESR	29.93 ± 24.34	27.40 ± 22.10	<0.05*	28.06 ± 23.03	27.55 ± 22.18	0.67
CRP	0.82 ± 1.39	0.71 ± 1.50	0.12	0.74 ± 1.18	0.72 ± 1.52	0.68

Values are presented as mean ± standard deviation or number (%). PSM: propensity score matching, BMI: body mass index, ACR: American college of rheumatology, USD: United States dollar, ACPA: anti-citrullinated peptide antibody, MTX: methotrexate, NSAID: non-steroidal anti-inflammatory drug, VAS: visual analog scale, GH: global health, DAS: disease activity score, ESR: erythrocyte sedimentation rate, EQ5D: EuroQol-5D, HAQ: health assessment questionnaire, CRP: C-reactive protein. *Asterisk values indicate statistical significance with $p<0.05$.

side effects, lower income, lower level of education, and greater use of biologics compared with the non-adherent group. The mean values of the physician's VAS score, DAS28-ESR, EQ5D, HAQ, and ESR were significantly higher in adherent group at baseline compared with non-adherent group. PSM was performed using a ratio of 1:3 as the baseline characteristics were significantly different between the two groups (Table 1). After PSM, 1,447 patients were allocated to the adherent group and 522 were allocated to the non-adherent group. Comparisons of the rate of EULAR response and disease flare between the two groups over three years are shown in Table 2. There were significantly more non-responders in the non-adherent group. Disease flares occurred more frequently in the non-adherent group, although the difference was not significant. Continuous variables related to treatment outcome over three years were not significantly different between the two groups; however, the DAS28-ESR scores at each follow-up tended to be higher in the non-adherent group compared with the adherent group (Table 3). We hypothesized that the effect of drug adherence would differ between early and late RA, and patients were classified into two groups according to disease duration of 48 months. A total of 843 patients were allocated to the early RA group, and 1,851 patients were allocated to the late RA group. We divided the early and late RA patients into adherent and non-adherent groups according to the previously defined criteria, and compared the outcomes after PSM with a ratio of 1:3. Table 4 shows the baseline characteristics of early and late RA patients after PSM. In the early RA group, there were significantly more good responders in the adherent group, whereas flare was more frequently reported in the late RA non-adherent group over three years (Table 2). The adherent group showed lower patient global health VAS score and DAS28-ESR score at the fourth follow-up in patients with early RA (Table 3); however, these findings were not observed in patients with late RA (Table 3). There was a serial change in global health VAS score and DAS28-ESR of patients over three years in early RA patients (Figure 2). In the adherent group, the patient's global health VAS score decreased constantly, while that of the non-adherent group decreased slightly then increased to the baseline level at the fourth follow-up. DAS28-ESR tended to decrease in both groups until the third follow-up, but rose again at the fourth follow-up in the non-adherent group.

DISCUSSION

This is the first large-scale study to report the effects of drug adherence on treatment outcome in Korean patients with RA over a long term observational period. EULAR response, disease flare, and other clinical outcomes that were related to treatment outcome were compared according to drug adherence. To evaluate drug adherence, we calculated the total number of days each patient failed to take medication using data collected over three years. We did not consider it appropriate to evaluate drug adherence using only one measurement as it is dynamic and not constant over time [7]. Drug adherence tended to be high during early-stage RA, but decreased as symptoms

Table 2. EULAR response and disease flare between the adherent and non-adherent groups over three years

Variable	Total population			Early RA			Late RA		
	Adherent (n=1,447)	Non-adherent (n=522)	p-value	Adherent (n=483)	Non-adherent (n=186)	p-value	Adherent (n=894)	Non-adherent (n=332)	p-value
EULAR response									
Good	302 (20.9)	93 (17.8)	0.14	135 (28.0)	38 (20.4)	<0.05*	160 (17.9)	53 (16.0)	0.45
Moderate	322 (22.3)	105 (20.1)	0.32	103 (21.3)	42 (22.6)	0.75	200 (22.4)	65 (19.6)	0.31
None	823 (56.9)	324 (62.1)	<0.05*	245 (50.7)	106 (57.0)	0.17	534 (59.7)	214 (64.5)	0.15
Disease flare									
FU2 flare	253 (17.5)	108 (20.7)	0.11	70 (14.5)	32 (17.2)	0.40	160 (17.9)	74 (22.3)	0.09
FU3 flare	265 (18.3)	102 (19.5)	0.56	79 (16.4)	32 (17.2)	0.82	158 (17.7)	69 (20.8)	0.22
FU4 flare	245 (16.9)	107 (20.5)	0.07	65 (13.5)	32 (17.2)	0.22	161 (18.0)	74 (22.3)	0.10
Any flare	511 (35.3)	203 (38.9)	0.15	147 (30.4)	59 (31.7)	0.78	317 (25.5)	142 (42.8)	<0.05*

Values are presented as number (%). Early and advanced RA was classified according to disease duration of 48 months. Flares were defined as any flare occurring during the follow-up period. EULAR: European league against rheumatism, RA: rheumatoid arthritis, FU2: second follow-up, FU3: third follow-up, FU4: fourth follow-up. *Asterisk values indicate statistical significance with $p < 0.05$.

Table 3. Comparisons of continuous variables related to treatment outcome between the adherent and non-adherent groups over 3 years

Variable	Total population			Early RA			Late RA		
	Adherent (n=1,447)	Non-adherent (n=522)	p-value	Adherent (n=483)	Non-adherent (n=186)	p-value	Adherent (n=894)	Non-adherent (n=332)	p-value
FU2									
Physician's VAS score	16.60±15.04	16.27±14.32	0.67	15.26±14.28	16.56±15.28	0.30	17.34±15.40	16.15±13.83	0.19
Patient's GH VAS score	35.07±24.30	36.85±24.13	0.15	31.05±23.04	35.80±25.75	<0.05*	37.42±24.42	37.30±23.24	0.94
DAS28-ESR	3.25±1.31	3.31±1.26	0.41	2.97±1.27	3.04±1.21	0.52	3.44±1.29	3.46±1.26	0.77
EQ5D	0.73±0.22	0.72±0.22	0.18	0.78±0.19	0.76±0.19	0.16	0.71±0.21	0.69±0.23	0.41
HAQ	0.52±0.58	0.51±0.57	0.52	0.36±0.46	0.37±0.50	0.82	0.62±0.60	0.58±0.59	0.26
ESR	25.77±21.57	26.50±23.02	0.51	23.55±21.02	22.73±19.46	0.64	27.05±21.46	28.68±24.49	0.26
CRP	0.72±2.95	0.59±1.00	0.33	0.94±5.11	0.55±0.82	0.30	0.64±1.02	0.62±1.10	0.83
FU3									
Physician's VAS score	15.88±13.51	15.62±12.81	0.70	15.54±13.03	15.19±12.76	0.75	16.27±14.02	15.62±12.17	0.45
Patient's GH VAS score	34.35±23.43	35.71±13.17	0.25	30.30±22.98	32.80±23.03	0.21	36.57±22.79	36.94±23.11	0.80
DAS28-ESR	3.19±1.26	3.21±1.20	0.79	2.93±1.20	2.96±1.17	0.75	3.34±1.25	3.33±1.19	0.87
EQ5D	0.73±0.22	0.75±0.20	0.07	0.77±0.21	0.80±0.20	0.10	0.71±0.21	0.72±0.20	0.30
HAQ	0.53±0.57	0.47±0.54	0.06	0.40±0.45	0.33±0.46	0.51	0.62±0.59	0.55±0.57	0.08
ESR	26.25±20.78	26.77±22.56	0.63	24.27±21.15	24.05±20.62	0.90	27.80±20.49	28.28±23.39	0.73
CRP	0.58±0.96	0.61±1.31	0.67	0.56±0.99	0.67±1.89	0.48	0.74±3.60	0.58±0.57	0.42
FU4									
Physician's VAS score	16.28±13.65	15.77±13.72	0.47	14.68±13.51	14.82±13.78	0.91	16.81±13.87	16.49±13.68	0.72
Patient's GH VAS score	35.06±23.93	33.32±25.79	0.13	29.40±22.21	35.22±24.03	<0.01*	38.32±23.83	38.18±24.26	0.92
DAS28-ESR	3.17±1.17	3.26±1.12	0.12	2.87±1.12	3.08±1.11	<0.05*	3.36±1.17	3.37±1.11	0.87
EQ5D	0.72±0.23	0.73±0.21	0.31	0.77±0.20	0.77±0.21	0.61	0.69±0.23	0.71±0.21	0.05
HAQ	0.57±0.61	0.53±0.59	0.15	0.38±0.47	0.38±0.48	0.87	0.68±0.64	0.61±0.63	0.11
ESR	26.26±20.33	26.41±18.90	0.88	23.54±19.04	24.85±20.16	0.43	28.33±21.46	27.36±18.30	0.43
CRP	0.78±2.92	0.86±4.69	0.62	0.62±1.17	1.25±7.74	0.27	0.72±1.37	0.67±0.99	0.54

Values are presented as mean±standard deviation. Early and advanced RA was classified according to disease duration of 48 months. RA: rheumatoid arthritis, VAS: visual analog scale, GH: global health, DAS: disease activity score, ESR: erythrocyte sedimentation rate, EQ5D: EuroQol-5D, HAQ: health assessment questionnaire, CRP: C-reactive protein, FU2: second follow-up, FU3: third follow-up, FU4: fourth follow-up. *Asterisk values indicate statistical significance with $p<0.05$.

improved. Pasma et al. [8] reported a decline in adherence over time in patients taking all types of disease-modifying anti-rheumatic drugs (DMARDs) except prednisolone. We measured total adherence by collecting data over three years to assess adherence throughout the entire study period.

Patients were classified into two groups according to drug adherence (adherence and non-adherence groups), and the baseline characteristics were found to be significantly different between the two groups. The non-adherent group was younger than the adherent group and had a shorter disease duration, fewer side effects, higher income, and higher level of education at baseline. Kim et al. [9] studied the prevalence and associated factors for non-adherence of Korean RA patients using the KORONA database. They performed multivariate regression analysis using various factors, and concluded that adverse events and higher levels of education were associated with non-adherence. Drug adherence is known to be affected by several factors in RA. A systemic review reported that drug adherence of RA patients is affected by various factors, such as age, sex, ethnicity, type

Table 4. Baseline characteristics between the adherent and non-adherent groups after propensity score matching using a ratio of 1:3 in early and late RA, according to disease duration of 48 months

Variable	Early RA			Late RA		
	Adherent (n=483)	Non-adherent (n=186)	p-value	Adherent (n=894)	Non-adherent (n=332)	p-value
Age (yr)	49.75±11.17	48.34±12.28	0.16	52.50±10.45	51.96±11.34	0.45
Sex, female	393 (81.4)	153 (82.3)	0.83	818 (91.5)	305 (91.9)	0.91
BMI	22.80±3.12	22.67±3.10	0.63	22.52±3.25	22.55±3.03	0.88
Disease duration (mo)	21.86±14.32	23.27±14.67	0.26	106.60±53.60	105.24±51.43	0.69
ACR criteria number						
<4	21 (4.3)	9 (4.8)	0.43	28 (3.1)	12 (3.6)	0.93
≥4	462 (95.7)	177 (95.2)		866 (96.9)	320 (96.4)	
Current smoker	50 (10.4)	19 (10.2)	0.73	42 (4.7)	16 (4.8)	0.96
Side effect	181 (37.5)	77 (41.4)	0.37	354 (39.6)	142 (42.8)	0.43
Income (USD/mo)						
<2,000	285 (59.0)	102 (54.8)	0.36	554 (62.0)	194 (58.4)	0.27
2000~4990	163 (33.7)	71 (38.2)		279 (31.2)	111 (33.4)	
≥5,000	35 (7.2)	13 (7.0)		61 (6.8)	27 (8.1)	
Education						
Middle school or less	163 (33.7)	320 (66.3)	0.22	348 (38.9)	546 (61.1)	0.26
High school or more	53 (28.5)	133 (71.5)		119 (35.8)	213 (64.2)	
Rheumatoid factor	346 (71.6)	133 (71.5)	1.00	642 (71.8)	241 (72.6)	0.83
ACPA	389 (80.5)	148 (79.6)	0.83	537 (60.1)	195 (58.7)	0.69
Medication						
MTX	421 (87.2)	157 (84.4)	0.38	776 (86.8)	291 (87.7)	0.77
NSAID	392 (81.2)	153 (82.3)	0.82	749 (83.8)	279 (84.0)	1.00
Steroid	405 (83.9)	156 (83.9)	1.00	741 (82.9)	274 (82.5)	0.87
Biologics	24 (5.0)	8 (4.3)	0.84	55 (6.2)	18 (5.4)	0.69
Physician's VAS	23.02±17.75	23.14±16.51	0.94	22.47±16.84	21.76±16.41	0.51
Patient's GH VAS	35.17±25.63	35.33±25.42	0.94	38.11±25.55	38.90±25.08	0.63
DAS28-ESR	3.49±1.34	3.49±1.34	0.97	3.70±1.27	3.62±1.27	0.29
EQ5D	0.74±0.22	0.75±0.23	0.73	0.70±0.21	0.70±0.24	0.79
HAQ	0.49±0.52	0.46±0.55	0.51	0.65±0.59	0.62±0.59	0.49
ESR	29.18±26.30	28.18±22.94	0.65	29.64±21.87	27.17±21.85	0.33
CRP	1.04±1.86	0.99±2.30	0.82	0.62±0.79	0.55±0.74	0.18

Values are presented as mean±standard deviation or number (%). RA: rheumatoid arthritis, BMI: body mass index, ACR: American college of rheumatology, USD: United States dollar, ACPA: anti-citrullinated peptide antibody, MTX: methotrexate, NSAID: non-steroidal anti-inflammatory drug, VAS: visual analog scale, GH: global health, DAS: disease activity score, ESR: erythrocyte sedimentation rate, EQ5D: EuroQol-5D, HAQ: health assessment questionnaire, CRP: C-reactive protein.

of medication, and disease duration [10]. Another systematic review showed that prior use of DMARDs and patient's beliefs about the medication were strongly related to medication adherence of RA patients [3]. Our data showed that the adherent group had higher DAS28 than the non-adherent group at baseline. It was reported that patients with acute-phase RA have relatively higher drug adherence compared with those with a stable disease state [11]. It is likely that high disease activity contributes to patients taking their medication regularly.

Our results showed that adherent RA patients had lower DAS28 and good response to medication, while non-adherence was related to poor response and disease flare over three years. Several studies have indicated that adherence is crucial for proper RA management. Adherent patients showed lower scores and greater improvement in DAS28, as well as more frequent and earlier sustained remission compared with non-adherent patients [12]. Adherence to MTX was associated with improving disease activity without increasing toxicity [13]. RA patients who were adherent to biologic agents had lower use of health care resources and steroids compared

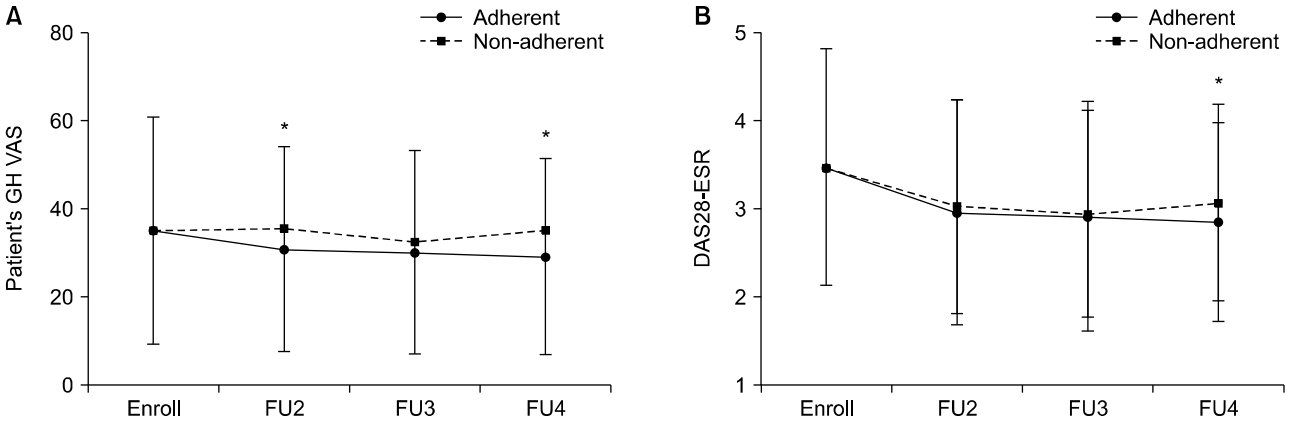

Figure 2. The change of patient's (A) GH VAS and (B) DAS28-ESR between two groups in early RA patients (mean ± standard deviation). GH VAS: global health visual analogue scale, DAS: disease activity score, ESR: erythrocyte sedimentation rate, FU2: second follow-up, FU3: third follow-up, FU4: fourth follow-up. *p-value <0.05.

with non-adherent patients [14]. Overall, adherent patients tended to have lower disease activity, more frequently sustained remission, and less radiographic progression compared with non-adherent patients [1,12,15]. The effect of adherence differed according to disease duration of RA. We classified the patients into early and late RA according to disease duration of 48 months by reviewing the previous study [2]. Our results showed that the effect of adherence was obvious in early RA patients with disease duration <4 years. Wabe et al. [16] in their study reported that adherence to DMARDs is associated with improvements in disease activity and functional outcomes in the first two years, but these effects were not replicated among existing DMARD users. A recently published Japanese study showed that changes in DAS28 and risk of disease flare were significantly lower in adherent patients with disease duration <4.6 years [2]. Tight disease control with regular medication might decrease disease activity and improve global health in early RA patients. In late patients with disease duration >4 years, these effects seemed to disappear. However, disease flare occurred more frequently in non-adherent patients. Disease flare was more occurred in non-adherent early RA patients, but the difference did not reach statistical significance. These findings imply that drug adherence is important in both the early and late RA. Non-adherence was previously reported to be associated with disease flare, as well as increased healthcare utilization and cost [17]. A previous study reported that development of erosive changes was more frequent in non-adherent patients than in adherent patients [12]. Consequently, non-adherent patients tended to incur higher medical costs and more severe structural damage than adherent patients.

The effect of adherence on DAS appears to be more prominent in the long term compared with the short term. Our data showed there were no differences in DAS28-ESR in early RA until the third follow-up, but there were discrepancies at the fourth follow-up. A previous study in an early RA cohort showed results that were consistent with ours. They observed 198 RA patients for three years, and found no significant association between adherence and DAS28 after one year, but the association reached significance after three years [15]. Unlike DAS28, drug adherence was not associated with improved physical function. Cannon et al. in their study found no significantly different changes in HAQ score between the adherent and non-adherent groups in an RA registry [18]. Our study also found no significant differences in HAQ score between the two groups over three years.

Our results indicate that improving adherence maximizes the response to medical treatment and reduces disease flare in patients with RA. A qualitative study suggested that good communication with healthcare providers, health professional support, and better explanation about treatment promoted better adherence to medication [19]. Another study reported that monitoring drug adherence and assessing disease activity and treatment outcome during the follow-up period could improve adherence [20]. New mobile technology could also contribute toward improving adherence in patients with RA. A recent meta-analysis reported that use of cell phone messaging applications was helpful in supporting the self-management of chronic disease [21]. In RA, cell

phone text messages were shown to significantly increase adherence to MTX [22]. In addition, regular phone calls by specialized nurses, better explanations about the reasons for taking medication, emails, and voice message reminders also contributed toward improving adherence [23].

The present study has several limitations. Firstly, a questionnaire was used to evaluate drug adherence. The questionnaire was simple, but may not have been the best method to evaluate drug adherence. Secondly, the proportion of adherent patients was relatively high compared with previous studies. It is possible that adherent patients who had a good relationship with their physicians may have been included in this cohort. Thirdly, non-adherent patients who were not followed up to three years were not included in this analysis. We could not find any significant differences in continuous variables between the two groups except patient's global health VAS score and DAS28-ESR over three years in early RA. Non-adherent patients who were lost during follow-up were not included in this analysis; therefore, the difference of continuous variables related to treatment outcome between two groups was not significant.

CONCLUSION

Adherent patients tended to have lower disease activity, particularly in early RA, whereas non-adherent patients were associated with non-response and higher disease flare rates. Improving adherence is necessary to increase treatment response and reduce disease flare.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Y.J.O. drafting of manuscript, B.H.P. analysis and interpretation of data. K.W.M. conception and design of study, acquisition of data, and revising the manuscript.

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