pISSN: 2093-940X, eISSN: 2233-4718
Journal of Rheumatic Diseases Vol. 25, No. 1, January, 2018
https://doi.org/10.4078/jrd.2018.25.1.47

Original Article

Prevalence and Associated Factors for Non-adherence in Patients with Rheumatoid Arthritis

Dam Kim[1,2], Ji-Young Choi[3], Soo-Kyung Cho[1,2], Chan-Bum Choi[1,2], So-Young Bang[4], Hoon-Suk Cha[5], Jung-Yoon Choe[6], Won Tae Chung[7], Seung-Jae Hong[3], Tae-Hwan Kim[1], Tae-Jong Kim[8], Eunmi Koh[5], Hye-Soon Lee[4], Jisoo Lee[9], Shin-Seok Lee[8], Sung Won Lee[7], Sung-Hoon Park[6], Seung-Cheol Shim[10], Dae-Hyun Yoo[1], Bo Young Yoon[11], Sang-Cheol Bae[1,2]*, Yoon-Kyoung Sung[1,2]*

[1]Hanyang University Hospital for Rheumatic Diseases, [2]Clinical Research Center for Rheumatoid Arthritis (CRCRA), [3]Kyung Hee University Medical Center, Seoul, [4]Hanyang University Guri Hospital, Guri, [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [6]Catholic University of Daegu School of Medicine, Daegu, [7]Dong-A University Hospital, Busan, [8]Chonnam National University Hospital, Gwangju, [9]Ewha Womans University Mokdong Hospital, Seoul, [10]Chungnam National University Hospital, Daejeon, [11]Inje University Ilsan Paik Hospital, Goyang, Korea

Objective. To estimate the prevalence of non-adherence to rheumatoid arthritis (RA) medication and identify the associated factors for non-adherence in RA patients. **Methods.** Among the KORean Observational study Network for Arthritis 3,523 patients who completed a questionnaire about the adherence to RA medication were analyzed. The patients were divided into two groups: 1) adherent group, patients who skipped medication ≤5 days within the past 2 months; and 2) non-adherent group, patients who skipped ≥6 days of medication. The baseline characteristics were compared, and multivariable regression analysis was performed to identify the associated factors for non-adherence. **Results.** The non-adherent group had 339 patients (9.6%). The common causes of non-adherence were forgetfulness (45.8%), absence of RA symptoms (24.7%), and discomfort with RA medication (13.1%). Younger age (odds ratio [OR] 1.02, $p<0.01$) and higher income (OR 1.70, $p<0.01$) were associated with an increased risk of non-adherence. Whereas higher functional disability (OR 0.68, $p<0.01$) and oral corticosteroid use (OR 0.73, $p=0.02$) were associated with a decreased risk of non-adherence. The associated factors differed according to cause of non-adherence. Having adverse events (OR 2.65, $p=0.02$) was associated with the risk of non-adherence due to discomfort with RA medication while a higher level of education (OR 2.37, $p=0.03$) was associated with the risk of non-adherence due to an absence of RA symptoms. **Conclusion.** The 9.6% of Korean RA patients were non-adherent to RA medication. The associated factors differed according to the cause of non-adherence. Therefore, an individualized approach will be needed to improve the adherence to RA medication. **(J Rheum Dis 2018;25:47-57)**

Key Words. Medication adherence, Arthritis, rheumatoid, Prevalence

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to joint destruction, disability and premature mortality [1]. Current treatment guidelines for RA recommend early aggressive management with disease-modifying anti-rheumatic drugs (DMARDs) [2]. The therapeutic approach for RA patients is mainly pharmacologic treatment, and therapeutic success is important for reducing symptoms, functional damage and joint deformity [3]. Therefore, RA patients require many pills that are DMARDs, corticosteroids, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). In addition, RA patients often have comorbidities due to the

Received : June 23, 2017, **Revised :** September 22, 2017, **Accepted :** October 17, 2017

Corresponding to : Yoon-Kyoung Sung, Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, 222 Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea. E-mail : sungyk@hanyang.ac.kr
Sang-Cheol Bae, Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, 222 Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea. E-mail : scbae@hanyang.ac.kr
*These authors contributed equally to this work.

disease's chronic inflammatory mechanism. Thus, polypharmacy is more common than for other chronic diseases [4], and patients can experience complications with their course of treatment.

Drug adherence is important because it can affect disease outcome [5]. Drug adherence is defined as the extent to which a patient's behavior matches what is prescribed by healthcare providers [6]. The word "compliance" was used previously, but this focused on patient's passive role in following a doctor's order. Therefore, "adherence" is preferred by healthcare providers. Adherence suggests a patient's rights in a therapeutic alliance or contract with their doctors [6,7]. Another term to explain the concept to taking medication is medication persistence which reflects continuously taking medications in a period of time [8].

Previous studies report that drug adherence of RA patients is vary according to studies and detection tools; about 30% estimated by medication event monitoring system (MEMS) to 80% by medication possession ratio and patient self-reported questionnaire [9-13]. In addition, many studies report that factors such as socioeconomics, disease-specific factors, and psychological factors are associated with drug adherence in RA patients [14-18]. However, most factors showed conflicting results. Considering that there are various causes of non-adherence in RA patients, we assumed that the associated factors for non-adherence also have to be analyzed according to the cause of non-adherence. Therefore, the purpose of this study was to estimate the prevalence of non-adherence to RA treatment in Korean RA cohort, and identify associated factors for non-adherence according to specific causes in RA patients.

MATERIALS AND METHODS

Study population

Patients aged 18 or older who satisfied the 1987 American College of Rheumatology classification criteria for RA were recruited by rheumatologists in 23 centers during routine clinic visits as part of the KORean Observational study Network for Arthritis (KORONA) [19]. KORONA is a nationwide prospective multicenter cohort which enrolls RA patients from 23 rheumatology centers. Among patients enrolled in KORONA, only one patient who did not complete a questionnaire about adherence to RA treatment was excluded in this study.

Prevalence and causes of non-adherence to RA treatment

We evaluated the prevalence of drug adherence using a self-reported questionnaire. The question "How many days did you fail to take your 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 31 days or more; and 6) not prescribed any medication. We defined the adherent group as patients who skipped medication ≤5 days within the past 2 months and the non-adherent group as patients who skipped ≥6 days. Patients who were not prescribed any medication were excluded from analysis (Figure 1).

In addition, we obtained the reasons for non-adherence to RA medication in a multiple-choice question: 1) for-

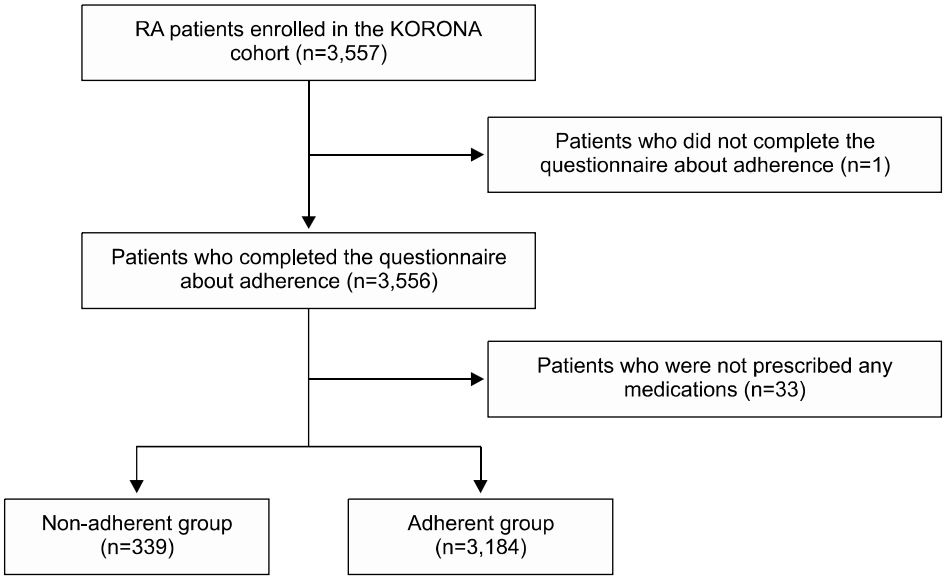

Figure 1. Patient selection flow chart. KORONA: KORean Observational study Network for Arthritis.

getfulness; 2) absence of RA symptoms; 3) discomfort with RA medication; 4) taking an alternative treatment for RA; or 5) other.

Associated factors for non-adherence to RA treatment

We collected information about patient demographic profiles and socioeconomic status including family income per month and level of education. Disease-specific information collected in detail included disease duration, disease activity defined as disease-activity score for 28 joints-erythrocyte sedimentation rate (DAS28-ESR), functional disability as a health assessment questionnaire (HAQ) and comorbidities. Experience of adverse events (AEs) was defined as the previous experience of any AEs since starting RA medication. Experience of AEs consisted of gastrointestinal (GI) AEs including stomachache, nausea/vomiting, dermatologic AEs such as alopecia, pruritus, and other AEs.

For medications, type of RA and osteoporotic medication and number of daily and weekly medications were collected. Detailed interviews and joint assessment were performed by rheumatologists or trained health professionals. Information about laboratory tests and medications were collected by medical chart review.

Review of literature about medication adherence in patients with RA

Systematic literature review of studies reporting medication adherence in patients with RA was performed in PubMed. Computerized search of database from their inception to March 17, 2017 was performed using key term of "arthritis, rheumatoid [MeSH Terms]" and "adherence [Title/Abstract] or compliance [Title/Abstract] or persistency [Title/Abstract]" in human subjects and articles written in English. In the table, studies with 100 patients or more were shown.

Ethical considerations

The study protocol was approved by the Institutional Review Board of Hanyang University Hospital (HYUH 2009-04-003, HYUH 2013-09-006) and other centers included in this study. Written informed consent was provided by each patient.

Statistical analysis

After estimating the prevalence of non-adherent group patients, we compared their demographic and clinical characteristics using chi-square tests and Student t-tests. To identify associated factors for non-adherence in RA patients, we performed crude and multivariable logistic regression analysis using socioeconomic and clinical information that can affect adherence to RA medication. Since there is no gold standard of definition for non-adherence, we performed a sensitivity analysis using a definition of non-adherent group as patients who skipped ≥ 16 days. And then we further analyzed associated factors for non-adherence due to absence of RA symptoms and discomfort with RA medication in non-adherent patients. All analyses were performed using IBM SPSS software version 20.0 (IBM Co., Armonk, NY, USA). Results were considered statistically significant when p-values were less than 0.05.

RESULTS

Patient characteristics

Mean age of patients in this study was 54.2 years and 85.7% were female (Table 1). Mean disease duration was 8.6 years and mean disease activity was 3.7 estimated by DAS28-ESR. In addition, 83.3% of patients were using methotrexate (MTX), and 5.9% were using biologic agents.

Prevalence of non-adherence

Among 3,523 patients included in analysis, 3,184 (90.4%) of RA patients were in the adherent group and 339 (9.6%) were in the non-adherent group (Table 1). Patients in the non-adherent group were younger (50.9±12.6 years, non-adherent vs. 54.6±11.7 years, adherent, $p<0.01$), and had higher income. More patients in the non-adherent group reported ever-experience of AEs (44.2% vs. 33.3%, $p<0.01$). In addition, patients in the non-adherent group had lower HAQ score (0.57±0.57 vs. 0.68±0.65, $p<0.01$), but fewer had hypertension (19.8% vs. 25.9%, $p=0.02$) or diabetes mellitus (DM) (3.5% vs. 8.5%, $p<0.01$) compared with the adherent group. Fewer patients in the non-adherent group were using oral corticosteroids (68.7% vs. 74.2%, $p=0.04$) or biologic agents (3.2% vs. 6.5%, $p=0.04$); MTX, other DMARDs, NSAIDs/painkillers, and the number of daily or weekly medications did not vary between the two groups.

We collected the cause of non-adherence to RA medication using a multiple-choice question (Figure 2). Common causes of non-adherence in the non-adherent group were forgetfulness (45.8%), absence of RA symptoms (24.7%), taking an alternative treatment for RA (14.6%), and dis-

Table 1. Demographic and clinical characteristics of study patients

Variable	Total patients (n=3,523)	Non-adherent group (n=339)	Adherent group (n=3,184)	p-value
Age (yr)	54.2±11.8	50.9±12.6	54.6±11.7	**<0.01**
Disease duration (yr)	8.6±7.6	8.5±6.8	8.6±7.6	0.82
Female sex	3,020 (85.7)	303 (89.4)	2,717 (85.3)	0.052
Income (US dollars/mo)				**<0.01**
<2,000	1,719 (49.0)	139 (41.1)	1,580 (49.8)	
2,000~4,990	1,394 (39.7)	143 (42.3)	1,251 (39.5)	
≥5,000	395 (11.3)	56 (16.6)	339 (10.7)	
Education				0.10
Middle school or less	1,601 (45.7)	140 (41.3)	1,461 (46.1)	
High school or more	1,906 (54.3)	199 (58.7)	1,707 (53.9)	
Adverse events	1,210 (34.3)	150 (44.2)	1,060 (33.3)	**<0.01**
DAS28-ESR	3.7±1.3	3.8±1.3	3.7±1.3	0.46
HAQ	0.67±0.64	0.57±0.57	0.68±0.65	**<0.01**
ESR	29.3±23.8	30.4±24.3	29.1±23.8	0.41
CRP	0.7±1.2	0.6±1.2	0.7±1.2	0.19
Comorbidities				
Cardiovascular disease	127 (3.6)	11 (3.2)	116 (3.6)	0.83
Hypertension	893 (25.3)	67 (19.8)	826 (25.9)	**0.02**
Pulmonary disease	326 (9.3)	29 (8.6)	297 (9.3)	0.71
Gastrointestinal disease	786 (22.3)	84 (24.8)	702 (22.0)	0.28
Hepatic disease	180 (5.1)	21 (6.2)	159 (5.0)	0.41
Renal disease	90 (2.6)	12 (3.5)	78 (2.4)	0.30
Diabetes mellitus	284 (8.1)	12 (3.5)	272 (8.5)	**<0.01**
Depression	56 (1.6)	10 (2.9)	46 (1.4)	0.06
Malignancy	102 (2.9)	10 (2.9)	92 (2.9)	1.00
Medication				
Methotrexate	2,935 (83.3)	286 (84.4)	2,649 (83.2)	0.64
Other DMARDs	2,755 (78.3)	266 (78.5)	2,489 (78.2)	0.99
NSAIDs/painkiller	2,840 (80.6)	275 (81.1)	2,565 (80.6)	0.86
Oral corticosteroid	2,594 (73.6)	233 (68.7)	2,361 (74.2)	**0.04**
Biologic agents	209 (5.9)	11 (3.2)	198 (6.2)	**0.04**
Anti-osteoporotic agents	843 (23.9)	69 (20.4)	774 (24.3)	0.12
Number of daily medications	2.6±1.0	2.6±1.0	2.7±1.0	0.14
Number of weekly medications	0.9±0.5	0.9±0.5	0.9±0.5	0.51
Dietary supplements	1,646 (46.7)	164 (48.4)	1,482 (46.6)	0.56

Values are presented as mean±standard deviation or number (%), and bold value indicates statistical significance at the 0.05 level. DAS28-ESR: disease activity score 28 joints-erythrocyte sedimentation rate, HAQ: health assessment questionnaire, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DMARDs: disease modifying anti-rheumatic drugs, NSAIDs: non-steroidal anti-inflammatory drugs.

comfort with RA medication (13.1%).

Associated factors for non-adherence in RA patients

To identify associated factors for non-adherence in RA patients, we performed crude and multivariable logistic regression analysis (Table 2). In crude analysis, younger age, female sex, and higher income were associated with non-adherence in RA patients. Patients who experienced GI AEs or with depression were at increased risk of non-adherence. Having hypertension or DM, or factors representing severe disease such as higher HAQ, or using oral corticosteroids or biologic agents were protective factors against non-adherence in RA patients.

After adjusting for variables, younger age (OR 1.02, 95% confidence interval [CI] 1.01~1.04, p<0.01), higher income (OR 1.71, CI 1.16~2.52 for income ≥5,000 dollars per month, p<0.01), experience of GI AEs (OR 1.83, CI 1.40~2.38, p<0.01), and higher DAS28-ESR (OR 1.13,

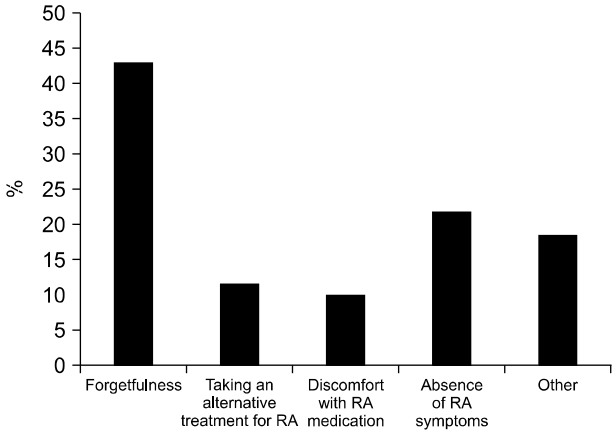

Figure 2. Causes of non-adherence in rheumatoid arthritis (RA) patients.

CI 1.01～1.26, p=0.03) were associated with increased the risk of non-adherence. Factors representing severe disease including higher functional disability (OR 0.67, CI 0.52～0.87, p＜0.01), and using oral corticosteroids (OR 0.73, CI 0.55～0.96, p=0.02) were associated with decreased risk of non-adherence. The results of analysis using definition of non-adherent group as patients who skipped ≥16 days were almost identical to the definition of non-adherence as patients who skipped ≥6 days (data not shown).

We further performed crude and multivariable regression analysis of associated factors for non-adherence according to intentional causes in non-adherent patients (Table 3). In adjusted analysis, having GI AEs (OR 2.44, CI 1.13～5.26, p=0.02) was associated with increased risk of non-adherence due to discomfort with RA medication. Higher level of education (OR 2.23, CI 1.03～4.81, p=0.04) was associated with increased risk of non-adherence due to absence of RA symptoms without medication.

DISCUSSION

In this study, 9.6% of RA patients were defined as non-adherent due to not taking their medication 6 or more days out of 60. Younger age, higher income, and experience of GI AEs were associated with increased risk of non-adherence. Having severe disease, as represented by higher functional disability and using oral corticosteroids, were associated with decreased risk of non-adherence in RA patients. Associated factors differed according to the cause of non-adherence: having GI AEs was associated with increased risk of non-adherence due to discomfort with RA treatment, while higher level of education was associated with increased risk of non-adherence due to absence of RA symptoms.

Previous studies reported about the adherence and associated factors affecting medication adherence in RA patients (Table 4) [9-18,20-29]. In these studies, adherence rate, the ways to estimate drug adherence, and definitions of adherence differed between studies. Although we expected that adherence rate estimated using electronic monitor such as MEMS will be lower than self-reported questionnaire, we could not find any definite difference of adherence rate in different ways to estimate drug adherence. The most feasible way to estimate drug adherence was self-reported measures. Compared to other measurement methods such as drug pill counts, electronic monitors, rates of refilling prescriptions, or sample assays of drug levels or drug byproducts, self-reported measures are easy, speedy, flexible and have low cost burden [6,30,31]. We used self-reported measures as two related questionnaires, and showed moderate correlation between the two questionnaires (data not shown). Among the questionnaires, we selected more objective questions that asked the number of days the patient failed to take their medication, and defined non-adherence failure to take medication 6 days or more.

Compared to previous studies, the adherence rate of 90.4% is quite high [9-18,20-29]. We assumed that this result was due to the characteristics of the patient cohort rather than our method of estimation. The patients in this cohort generally have good relationships with doctors, have insight into their disease, and are cooperative. As such, they may have good adherence to medication.

Similar to a previous study that reported that older patients have higher adherence and patients who are busy tend to have lower adherence [14,32], we found that younger age was associated with non-adherence in RA patients. In this study, experiencing AEs was also associated with non-adherence in RA patients. We propose that experiencing AEs affects beliefs about medications, such as the general harm of medications, which are associated with drug adherence [10,16]. In contrast, variables that represent severe disease such as higher HAQ and use of oral corticosteroids had protective effects against non-adherence; these results were consistent with previous studies [16,32]. Interestingly, higher DAS28-ESR was associated with non-adherence; in contrast, higher HAQ and use of oral corticosteroids were protective factors against non-adherence. Since it is well-known that

Table 2. Associated factors for non-adherence in RA patients

Variable	Crude		Multivariable (1)		Multivariable (2)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Younger age (yr)	1.03 (1.02～1.04)	**<0.01**	1.02 (1.01～1.04)	**<0.01**	1.02 (1.01～1.04)	**<0.01**
Disease duration (yr)	1.00 (0.98～1.01)	0.82				
Female sex	1.45 (1.01～2.07)	**0.04**	1.27 (0.84～1.91)	0.25	1.25 (0.83～1.88)	0.29
Income (US dollars/mo)						
<2,000	Reference		Reference		Reference	
2,000～4,990	1.30 (1.02～1.66)	**0.04**	1.16 (0.87～1.56)	0.31	1.15 (0.86～1.55)	0.34
≥5,000	1.88 (1.35～2.62)	**<0.01**	1.70 (1.15～2.52)	**<0.01**	1.71 (1.16～2.52)	**<0.01**
Education						
Middle school or less	Reference		Reference		Reference	
High school or more	1.22 (0.97～1.53)	0.09	0.73 (0.53～1.01)	0.054	0.72 (0.53～0.997)	**0.048**
Adverse events	1.59 (1.27～2.00)	**<0.01**	1.78 (1.38～2.29)	**<0.01**		
Gastrointestinal adverse events	1.72 (1.36～2.17)	**<0.01**			1.83 (1.40～2.38)	**<0.01**
Dermatologic adverse events	1.39 (0.97～1.98)	0.07			1.28 (0.88～1.88)	0.2
Other adverse events	0.67 (0.43～1.03)	0.07			1.35 (0.84～2.15)	0.21
DAS28-ESR	1.04 (0.95～1.13)	0.46	1.13 (1.01～1.27)	**0.03**	1.13 (1.01～1.26)	**0.04**
HAQ	0.75 (0.62～0.91)	**<0.01**	0.68 (0.52～0.88)	**<0.01**	0.67 (0.52～0.87)	**<0.01**
ESR	1.00 (1.00～1.01)	0.41				
CRP	0.93 (0.83～1.04)	0.20				
Comorbidities						
Cardiovascular disease	0.89 (0.47～1.66)	0.71				
Hypertension	0.70 (0.53～0.93)	**0.01**	0.97 (0.70～1.34)	0.83	0.97 (0.70～1.35)	0.87
Pulmonary disease	0.91 (0.61～1.36)	0.64				
Gastrointestinal disease	1.17 (0.90～1.51)	0.25	1.01 (0.75～1.35)	0.96	0.98 (0.73～1.32)	0.88
Hepatic disease	1.26 (0.79～2.01)	0.34				
Renal disease	1.46 (0.79～2.71)	0.23				
Diabetes mellitus	0.39 (0.22～0.71)	**<0.01**	0.51 (0.27～0.99)	**0.048**	0.51 (0.27～0.99)	**0.048**
Depression	2.07 (1.04～4.15)	**0.04**	2.02 (0.95～4.26)	0.07	1.95 (0.92～4.14)	0.08
Malignancy	1.02 (0.53～1.98)	0.95				
Medication						
Methotrexate	1.09 (0.80～1.48)	0.58				
Other DMARDs	1.01 (0.77～1.33)	0.93				
NSAIDs/painkiller	1.04 (0.78～1.38)	0.80	1.21 (0.87～1.69)	0.25	1.21 (0.87～1.69)	0.26
Oral corticosteroid	0.77 (0.60～0.98)	**0.03**	0.73 (0.55～0.96)	**0.02**	0.73 (0.55～0.96)	**0.02**
Biologic agents	0.51 (0.27～0.94)	**0.03**	0.54 (0.29～1.02)	0.06	0.53 (0.28～1.00)	0.051
Anti-osteoporotic agents	0.80 (0.60～1.05)	0.11				
Number of daily medications	0.92 (0.83～1.03)	0.15				
Number of weekly medications	0.93 (0.74～1.16)	0.51				
Dietary supplements	1.08 (0.86～1.35)	0.52				

Values are presented as mean±standard deviation or number (%), and bold value indicates statistical significance at the 0.05 level. RA: rheumatoid arthritis, OR: odds ratio, CI: confidence interval, DAS28-ESR: disease activity score 28 joints-erythrocyte sedimentation rate, HAQ: health assessment questionnaire, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DMARDs: disease modifying anti-rheumatic drugs, NSAIDs: non-steroidal anti-inflammatory drugs.

high disease activity is associated with the use of oral corticosteroids or high disability measured by high HAQ score [33,34], this result was somewhat surprising. Several studies report conflicting results with regard to disease activity [5,32]. In one study, higher disease activity was a predictive factor for drug adherence. On the other hand, another study found that non-adherence leads to high disease activity. Since our study has a cross-sectional design, higher disease activity as an associated factor for non-adherence could be the result of non-adherence. Moreover, our multivariable analyses of associated factors for non-adherence due to each cause showed that

Table 3. Associated factors for non-adherence due to each cause in non-adherent RA patients.

Variable	Discomfort with RA medications				Absence of RA symptoms			
	Multivariable (1)		Multivariable (2)		Multivariable (1)		Multivariable (2)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Younger age (yr)	1.00 (0.96～1.03)	0.82	1.01 (0.97～1.05)	0.68	0.95 (0.92～0.98)	**<0.01**	0.95 (0.92～0.98)	**<0.01**
Female sex	3.34 (0.41～26.94)	0.26	3.27 (0.40～26.55)	0.27	1.17 (0.47～2.94)	0.74	1.16 (0.47～2.92)	0.75
Income (US dollars/mo)								
<2,000	Reference		Reference		Reference		Reference	
2,000～4,990	1.08 (0.45～2.63)	0.86	1.08 (0.44～2.63)	0.88	1.60 (0.80～3.17)	0.18	1.60 (0.80～3.18)	0.18
≥5,000	0.70 (0.21～2.35)	0.56	0.72 (0.21～2.49)	0.61	1.69 (0.70～4.11)	0.24	1.64 (0.68～4.00)	0.27
Education								
Middle school or less	Reference		Reference		Reference		Reference	
High school or more	0.95 (0.36～2.53)	0.92	0.95 (0.36～2.53)	0.92	2.37 (1.10～5.12)	**0.03**	2.23 (1.03～4.81)	**0.04**
Adverse events	2.65 (1.21～5.81)	**0.02**			0.51 (0.28～0.94)	**0.03**		
Gastrointestinal adverse events			2.44 (1.13～5.26)	**0.02**			0.51 (0.27～0.96)	**0.04**
Dematologic adverse events			1.64 (0.59～4.56)	0.34			1.06 (0.42～2.67)	0.91
Other adverse events			1.54 (0.45～5.29)	0.50			1.12 (0.41～3.01)	0.83
Enrollment								
DAS28-ESR	1.04 (0.74～1.48)	0.82	1.05 (0.74～1.49)	0.80	1.04 (0.79～1.36)	0.78	1.03 (0.79～1.35)	0.83
HAQ	1.97 (0.93～4.18)	0.08	1.90 (0.89～4.09)	0.10	0.69 (0.35～1.35)	0.28	0.68 (0.35～1.35)	0.27
Comorbidities								
Hypertension	2.01 (0.88～4.58)	0.10	1.98 (0.89～4.09)	0.10	0.94 (0.46～1.94)	0.87	0.87 (0.42～1.79)	0.7
Gastrointestinal disease	1.77 (0.81～3.86)	0.15	1.74 (0.78～3.89)	0.18	1.07 (0.55～2.06)	0.85	1.14 (0.58～2.21)	0.71
Diabetes mellitus	0.69 (0.07～6.91)	0.75	0.76 (0.08～7.44)	0.82	0.78 (0.15～4.14)	0.77	0.80 (0.15～4.23)	0.79
Depression	1.54 (0.16～15.21)	0.71	1.65 (0.17～16.44)	0.67	1.61 (0.35～7.29)	0.54	1.78 (0.39～8.18)	0.46
Medication								
NSAIDs/painkiller	0.32 (0.13～0.77)	**0.01**	0.32 (0.13～7.78)	**0.01**	1.03 (0.49～1.55)	0.93	0.96 (0.46～2.03)	0.92
Oral corticosteroid	1.47 (0.62～3.48)	0.38	1.55 (0.65～3.71)	0.33	0.84 (0.46～1.55)	0.58	0.83 (0.45～1.53)	0.56
Biologic agents	1.74 (0.37～8.07)	0.48	1.58 (0.33～7.58)	0.57	0.67 (0.13～3.52)	0.64	0.64 (0.12～3.43)	0.60

Values are presented as mean±standard deviation or number (%), and bold value indicates statistical significance at the 0.05 level. RA: rheumatoid arthritis, OR: odds ratio, CI: confidence interval, DAS28-ESR: disease activity score 28 joints-erythrocyte sedimentation rate, HAQ: health assessment questionnaire, NSAIDs: non-steroidal anti-inflammatory drugs.

Table 4. Literature review of medication adherence in patients with RA

Study	Year	Country	Patients (n)	Study design	Medication	Method	Definition of adherence	Adherence rate
van den Bemt et al. [10]	2009	Netherland	228	Cross-sectional design	DMARDs	CQR	≥80%	68%
						MARS	>23	60%
Salt et al. [9]	2010	USA	108	Cross-sectional design	RA medication	MARS-9	≥Score 39	91%
Cannon et al. [12]	2011	USA	455	Longitudinal study	MTX	MPR	≥0.8	81%
Waimann et al. [11]	2013	USA	102	Longitudinal study	DMARDs and prednisone	MEMS	≥80%	21% for DMARDs, 41% for prednisone
Zwikker et al. [20]	2014	Netherland	575	Cross-sectional design	DMARDs	CQR	≥80%	70%
DiBenedetti et al. [21]	2015	USA	501	Cross-sectional design	MTX	Patient self-reported questionnaire	Took all MTX doses	42%
Pasma et al. [22]	2015	Netherland	120	Longitudinal study	DMARDs	MEMS	≥80%	91%～69% for MTX, 80%～54% for SSZ
Kumar et al. [23]	2015	UK	180	Cross-sectional design	DMARDs	MARS-6	≥Score 26	68%
De Cuyper et al. [24]	2016	Belgium	129	Cross-sectional design	MTX	MEMS	Took all MTX doses	58%
Curtis et al. [13]	2016	USA	228	Cross-sectional design	MTX	Patient self-reported questionnaire "In the last 4 weeks, how many weekly doses of methotrexate do you think that you have taken?"	Took all MTX doses	80%
Brandstetter et al. [25]	2016	Germany	361	Cross-sectional design	RA medication	MARS	≥Score 24	47%
Xia et al. [26]	2016	China	129	Cross-sectional design	DMARDs	CQR	≥80%	38%
Michetti et al. [27]	2017	Multi-country	1,981	Cross-sectional design	DMARDs	MMAS-4	4	Approximately 53%
Pasma et al. [28]	2017	Netherland	206 (74.2% RA)	Longitudinal study	DMARDs, steroid	MEMS	≥80%	>75%
Wabe et al. [29]	2017	Australia	111	Longitudinal study	DMARDs	PDC	≥80%	46%
Kim et al. [present study]	2017	Korea	3,523	Cross-sectional design	Anti-RA medication	Patient self-reported questionnaire "How many days did you fail to take your medication in the preceding 60 days?"	Took ≥ 55 days in 60 days (92%)	90.4%

RA: rheumatoid arthritis, DMARDs: disease modifying anti-rheumatic drugs, CQR: compliance questionnaire on rheumatology, MARS: medication adherence report scale, MTX: methotrexate, MPR: medication possession ratio, MEMS: medication event monitoring system, SSZ: sulfasalazine, MMAS-4: the four-item Morisky Medication Adherence Scale, PDC: proportion of days covered.

DAS28-ESR and HAQ had different effects on non-adherence according to the cause.

Several studies investigated polypharmacy in RA and other diseases [10,16,35]. The studies showed conflicting results about associations between polypharmacy and drug adherence. We also analyzed the effect of the number of daily and weekly medications and dietary supplements on drug adherence; we found no association between them.

To find causes of non-adherence, non-adherence can be divided into two subtypes: unintentional (due to forgetfulness, regimen complexity or physical problems) and intentional (based on the patient's decision to take no/less medication) [18]. In this study, forgetfulness was most frequent cause of non-adherence. In addition, many patients showed intentional non-adherence, discomfort with RA medication or absence of RA symptoms. According to a previous review, patients with intentional nonadherence may make a benefit-risk analysis, weighing the perceived risks of treatment against the perceived benefits [18]. We assumed that demographic and clinical characteristics would be different between patients who experienced discomfort with RA medication and absence of RA symptoms. Thus, we further analyzed factors associated with non-adherence due to specific causes.

As we hypothesized, factors associated with non-adherence for each cause differed. Experiencing GI AEs was associated with increased risk of non-adherence due to discomfort with RA medication, while GI AEs had protective effects against non-adherence due to the absence of RA symptoms. Although the questionnaire asking cause of non-adherence was multiple-choice question, patients who experience AEs tend to choose 'AEs due to RA medication' as the cause of non-adherence (data not shown). In addition, having NSAIDs/painkillers showed protective effects against non-adherence due to discomfort with RA medication, but no significant association was seen between any medication and non-adherence due to the absence of RA symptoms. More patients without NSAIDs/painkillers identified the cause of their non-adherence as 'AEs due to RA medication' than patients with NSAIDs/painkillers, while there was no difference in 'absence of RA symptoms'.

Among comorbidities, only DM showed positive effect on adherence. We think there are two possibilities. First, DM and RA are chronic diseases which need regular medication regardless of symptoms. Therefore, patients with DM and RA undergo frequent education about medication. Second, RA patients with glucocorticoid, which increase the blood glucose level, are strictly educated to have regular medication of DM from their doctor. This careful management can have positive effect of medication adherence. However, the relationship has to be revealed in future study. Differences in associated factors for non-adherence due to all causes, older age and higher level of education were associated with risk of non-adherence due to absence of RA symptoms. Although many studies found that younger age is associated with non-adherence but education was not [15,16], we also know that patient knowledge, self-efficacy, and beliefs about the disease and its treatment influence adherence [10,15,16]. Therefore, among intentional non-adherence, especially when RA symptoms were absent without medication, patients with more experience and knowledge weigh benefits and risks for RA treatment and then decide not to take medicine.

In this study, we found that causes of non-adherence varied and differed according to patient profile and disease status. Thus, uniform efforts to raise adherence could cause the reverse effect. Considering our results, we suggest patient education or reminder systems for patients who tend to be forgetful about medication. In addition, for patients who experience GI AEs, we should prescribe a more careful combination of medications or doses to minimize AEs. In patients without RA symptoms, rapid decreases in medication through doctor-patient communication are needed, especially for patients who are young and have high levels of education.

This study has several strengths. First, we analyzed associated factors for non-adherence according to causes, and found that associated factors differed according to the cause of non-adherence. We assert that non-adherence must be considered on an individual basis. Second, compared to previous studies, we used a larger observational cohort that could better represent the RA patient population. However, we also had several limitations. First, self-reported questionnaires were used to identify adherence in RA patients. This method is useful for large groups of patients, but is not as accurate as other objective methods. Second, since our study had a cross-sectional design, we could not report definite causal relationships between several associated factors and non-adherence. Further study is needed using a prospective study design for conclusive results.

CONCLUSION

In conclusion, 9.6% of RA patients were non-adherent to medication. Associated factors for non-adherence differed according to causes. Thus, an individualized approach according to the cause of non-adherence is needed to improve adherence.

ACKNOWLEDGMENTS

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number. HI16C0061).

CONFLICT OF INTEREST

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

REFERENCES

1. Firestein GS. Evolving concepts of rheumatoid arthritis. Nature 2003;423:356-61.
2. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012;64:625-39.
3. Kuriya B, Xiong J, Boire G, Haraoui B, Hitchon C, Pope J, et al. Earlier time to remission predicts sustained clinical remission in early rheumatoid arthritis--results from the Canadian Early Arthritis Cohort (CATCH). J Rheumatol 2014;41:2161-6.
4. Treharne GJ, Douglas KM, Iwaszko J, Panoulas VF, Hale ED, Mitton DL, et al. Polypharmacy among people with rheumatoid arthritis: the role of age, disease duration and comorbidity. Musculoskeletal Care 2007;5:175-90.
5. Contreras-Yáñez I, Ponce De León S, Cabiedes J, Rull-Gabayet M, Pascual-Ramos V. Inadequate therapy behavior is associated to disease flares in patients with rheumatoid arthritis who have achieved remission with disease-modifying antirheumatic drugs. Am J Med Sci 2010;340:282-90.
6. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97.
7. Horne R. Compliance, adherence, and concordance: implications for asthma treatment. Chest 2006;130(1 Suppl): 65S-72S.
8. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. Value Health 2008;11: 44-7.
9. Salt E, Frazier SK. Adherence to disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a narrative review of the literature. Orthop Nurs 2010;29: 260-75.
10. van den Bemt BJ, van den Hoogen FH, Benraad B, Hekster YA, van Riel PL, van Lankveld W. Adherence rates and associations with nonadherence in patients with rheumatoid arthritis using disease modifying antirheumatic drugs. J Rheumatol 2009;36:2164-70.
11. Waimann CA, Marengo MF, de Achaval S, Cox VL, Garcia-Gonzalez A, Reveille JD, et al. Electronic monitoring of oral therapies in ethnically diverse and economically disadvantaged patients with rheumatoid arthritis: consequences of low adherence. Arthritis Rheum 2013;65: 1421-9.
12. Cannon GW, Mikuls TR, Hayden CL, Ying J, Curtis JR, Reimold AM, et al. Merging Veterans Affairs rheumatoid arthritis registry and pharmacy data to assess methotrexate adherence and disease activity in clinical practice. Arthritis Care Res (Hoboken) 2011;63:1680-90.
13. Curtis JR, Bharat A, Chen L, Greenberg JD, Harrold L, Kremer JM, et al. Agreement between rheumatologist and patient-reported adherence to methotrexate in a US rheumatoid arthritis registry. J Rheumatol 2016;43:1027-9.
14. Park DC, Hertzog C, Leventhal H, Morrell RW, Leventhal E, Birchmore D, et al. Medication adherence in rheumatoid arthritis patients: older is wiser. J Am Geriatr Soc 1999;47: 172-83.
15. Brus H, van de Laar M, Taal E, Rasker J, Wiegman O. Determinants of compliance with medication in patients with rheumatoid arthritis: the importance of self-efficacy expectations. Patient Educ Couns 1999;36:57-64.
16. Treharne GJ, Lyons AC, Kitas GD. Medication adherence in rheumatoid arthritis: effects of psychosocial factors. Psychol Health Med 2004;9:337-49.
17. Viller F, Guillemin F, Briançon S, Moum T, Suurmeijer T, van den Heuvel W. Compliance to drug treatment of patients with rheumatoid arthritis: a 3 year longitudinal study. J Rheumatol 1999;26:2114-22.
18. van den Bemt BJ, Zwikker HE, van den Ende CH. Medication adherence in patients with rheumatoid arthritis: a critical appraisal of the existing literature. Expert Rev Clin Immunol 2012;8:337-51.
19. Sung YK, Cho SK, Choi CB, Park SY, Shim J, Ahn JK, et al. Korean Observational Study Network for Arthritis (KORONA): establishment of a prospective multicenter cohort for rheumatoid arthritis in South Korea. Semin Arthritis Rheum 2012;41:745-51.
20. Zwikker HE, van Dulmen S, den Broeder AA, van den Bemt BJ, van den Ende CH. Perceived need to take medication is associated with medication non-adherence in patients with rheumatoid arthritis. Patient Prefer Adherence 2014;8: 1635-45.
21. DiBenedetti DB, Zhou X, Reynolds M, Ogale S, Best JH. Assessing methotrexate adherence in rheumatoid arthritis: a cross-sectional survey. Rheumatol Ther 2015;2:73-84.
22. Pasma A, Schenk CV, Timman R, Busschbach JJ, van den Bemt BJ, Molenaar E, et al. Non-adherence to disease-modifying antirheumatic drugs is associated with higher disease activity in early arthritis patients in the first year of the disease. Arthritis Res Ther 2015;17:281.

23. Kumar K, Raza K, Nightingale P, Horne R, Chapman S, Greenfield S, et al. Determinants of adherence to disease modifying anti-rheumatic drugs in White British and South Asian patients with rheumatoid arthritis: a cross sectional study. BMC Musculoskelet Disord 2015;16:396.
24. De Cuyper E, De Gucht V, Maes S, Van Camp Y, De Clerck LS. Determinants of methotrexate adherence in rheumatoid arthritis patients. Clin Rheumatol 2016;35:1335-9.
25. Brandstetter S, Riedelbeck G, Steinmann M, Loss J, Ehrenstein B, Apfelbacher C. Depression moderates the associations between beliefs about medicines and medication adherence in patients with rheumatoid arthritis: Cross-sectional study. J Health Psychol 2016 May 1 [Epub]. DOI: 10.1177/1359105316646440.
26. Xia Y, Yin R, Fu T, Zhang L, Zhang Q, Guo G, et al. Treatment adherence to disease-modifying antirheumatic drugs in Chinese patients with rheumatoid arthritis. Patient Prefer Adherence 2016;10:735-42.
27. Michetti P, Weinman J, Mrowietz U, Smolen J, Peyrin-Biroulet L, Louis E, et al. Impact of treatment-related beliefs on medication adherence in immune-mediated inflammatory diseases: results of the global ALIGN study. Adv Ther 2017;34:91-108.
28. Pasma A, Schenk C, Timman R, van 't Spijker A, Appels C, van der Laan WH, et al. Does non-adherence to DMARDs influence hospital-related healthcare costs for early arthritis in the first year of treatment? PLoS One 2017;12:e0171070.
29. Wabe N, Lee A, Wechalekar M, McWilliams L, Proudman S, Wiese M. Adherence to combination DMARD therapy and treatment outcomes in rheumatoid arthritis: a longitudinal study of new and existing DMARD users. Rheumatol Int 2017;37:897-904.
30. Koneru S, Shishov M, Ware A, Farhey Y, Mongey AB, Graham TB, et al. Effectively measuring adherence to medications for systemic lupus erythematosus in a clinical setting. Arthritis Rheum 2007;57:1000-6.
31. Rapoff MA, Belmont JM, Lindsley CB, Olson NY. Electronically monitored adherence to medications by newly diagnosed patients with juvenile rheumatoid arthritis. Arthritis Rheum 2005;53:905-10.
32. Tuncay R, Eksioglu E, Cakir B, Gurcay E, Cakci A. Factors affecting drug treatment compliance in patients with rheumatoid arthritis. Rheumatol Int 2007;27:743-6.
33. Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001;44:2009-17.
34. Choi SC, Ingale SL, Kim JS, Park YK, Kwon IK, Chae BJ. An antimicrobial peptide-A3: effects on growth performance, nutrient retention, intestinal and faecal microflora and intestinal morphology of broilers. Br Poult Sci 2013;54:738-46.
35. Wawruch M, Zatko D, Wimmer G Jr, Luha J, Hricak V Jr, Murin J, et al. Patient-related characteristics associated with non-persistence with statin therapy in elderly patients following an ischemic stroke. Pharmacoepidemiol Drug Saf 2017;26:201-7.