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Study of Drug Adherence in a Large Japanese Population with Rheumatoid Arthritis: Epidemiological Survey Focused on District and Subject Ages



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ABSTRACT

Objective: Drug therapy is a key to the treatment of rheumatoid arthritis (RA) and is essential for every patient. However, data regarding drug adherence in Japan are currently limited. Identifying real situations regarding adherence can help in the choice of therapy for individual patients. We studied the adherence of patients with RA in Japan using a questionnaire. Methods: We conducted a survey of adherence for patients with RA with the cooperation of a patients' association. Five thousand questionnaires were distributed in all prefectures in Japan from 2012-2013. Results: Valid responses were received from 3063 participants (61.3%). There were no significant differences in adherence by district in Japan. In every prefecture, self-assessment of adherence was 75% or higher for every drug, including anti-RA drugs, nonsteroidal anti-inflammatory drugs or steroids, and other drugs. The elderly (>70 years) tended to forget to take drugs more often than younger patients (<50). In addition, older patients tended to take more concomitant drugs in addition to those for RA compared with younger patients. Conclusion: Because patients with RA are living longer lives, it is important to track adherence to therapy. Understanding true rates of adherence may help in the choice of drug for some patients and allow for healthcare providers' support to encourage adherence.



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INTRODUCTION

Many studies have examined adherence to medication in patients with chronic diseases. Most reports have shown that only 50-60% of patients take medicine as prescribed [1-8]. Poor adherence affects not only therapy but leads to additional medical costs [9, 10]. For example, the doctor in charge may change therapy to a new drug or prescribe a higher dose if no effects are seen, believing that the patient is taking the medication regularly. Thus patients may not be prescribed the best drug or dose for their condition. Poor adherence also leads to higher costs, including medical insurance expenses and patients' payments. If patients undergo multiple medical checkups and take multiple drugs, poor adherence to therapy may cause secondary effects. Thus the problems of adherence and drug management are important in terms of therapeutic appropriateness and cost-effectiveness in medical care [11, 12].

Currently the treatment options for rheumatoid arthritis (RA) have grown, and patients have many choices, including oral medicines, infusions, and self-injections. In most cases, patients require a combination of different therapies [13-15]. To improve outcomes in patients with RA, it is necessary to understand adherence to drug therapy among patients in a community setting. Currently, no large study has examined adherence to RA therapy in Japan, which makes it difficult to assess the effectiveness of therapy. Furthermore, physicians may find it useful to understand the patient's lifestyle and likelihood of adhering to therapy when choosing the most appropriate treatment and support for patients.

The aim of this study was to estimate true drug adherence among patients with RA in Japan. A simple questionnaire survey was conducted with the cooperation of the Japanese RA Patients' Association (JRPA: Japanese name as Nihonn Ryumachi Tomonokai).

MATERIALS AND METHODS

Subjects

In November 2012, we received notice from the JRPA, which had been provided with an explanation of the aim of the study and information on how it would be conducted, that they would help with the survey in terms of providing access to patient's addresses. In December 2012, we sent a simple questionnaire printed on prepaid reply postcards to 5000 randomly selected subjects from the JRPA list to subjects in all prefectures in Japan. A balanced

distribution of the number of patients in each prefecture was determined with the support of executives of the JRPA.

Questionnaire

To avoid identification of subjects, all questionnaires (postcards) were enclosed in envelopes with an explanatory note from the JRPA and assurance that data were to be used only to analyze adherence to RA medications. The questionnaire included 10 items, including items on demographics and drug adherence. In addition, we provided space for comments (Table 1). Participants were told that returning the postcard represented informed consent, that responses were anonymous, and that all postcards would be used only for this study. In this paper, we focused on differences in adherence between districts and subject ages. Questionnaires were collected until the end of February 2013.

Table 1. Questionnaire about drug taking^a

Please check under each question (? , / , ○)

1. Age 1. <50 2. 50-59 3. 60-69 4. >70
2. Sex 1. Female 2. Male
3. Who manages your drugs 1. Yourself 2. Family or helper 3. Others
4. How many drugs do you take beside drugs for rheumatoid arthritis (RA) 1. None 2. 1-3 3. More than 4
5. Frequency of non-adherence (forgetting to take drugs)^b
6. Control of amount of drugs
 1. Take drugs according to prescription
 2. Change amount of drugs depending on physical condition
7. Use of reminder to avoid missing a dose
 1. None
 2. Use subdivided drug container
 3. Use calendar type container
 4. Other
8. Have you experienced difficulty opening (using) drug packages? [You can check multiple items]
 1. None
 2. Pill, Capsule
 3. Powder, Granule
 4. Suppository
 5. Other
9. Your prefecture: _____
10. Free comments:

^b: Frequency of non-adherence

5-1. Anti-RA drugs	5-2. Steroids [*] , NSAIDs	5-3. Others
1. 0-2/M (Month)	1. 0-2/M	1. 0-2/M
2. 1/W (Week)	2. 1/W	2. 1/W
3. 2/W (Week)	3. 2/W	3. 2/W
4. More than 3/W	4. More than 3/W	4. More than 3/W

^a: Questions were contained on a prepaid postcard. Subjects were asked to place a checkmark under each appropriate response.

^b: 5. Detailed data regarding frequency of non-adherence is shown in the table below.

Statistical analysis

Statistical analysis was performed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA). Inter-group analyses were performed using Student's t-test. *P* values less than 0.05 were considered significant.

RESULTS

Table 2 and Figure 1 show the distribution and response number of questionnaires. The overall response rate was 3467 (69.3%); however, after removing responses with invalid answers, the final response rate was 3063 (61.3%) of returned answers. There were no differences in the number of valid responses based on divided block areas in Japan from north to south (Table 2).

Table 3 shows the number of returned questionnaires by prefecture. Although there were differences in the number of JRPA members by prefecture, we accounted for these differences during questionnaire distribution. Thus, we received responses from subjects in every prefecture of Japan. Table 4 shows the characteristics of respondents by age and sex. Most respondents (92.2%) were female, and the greatest numbers were aged 60 to 69 or aged 70 and older.

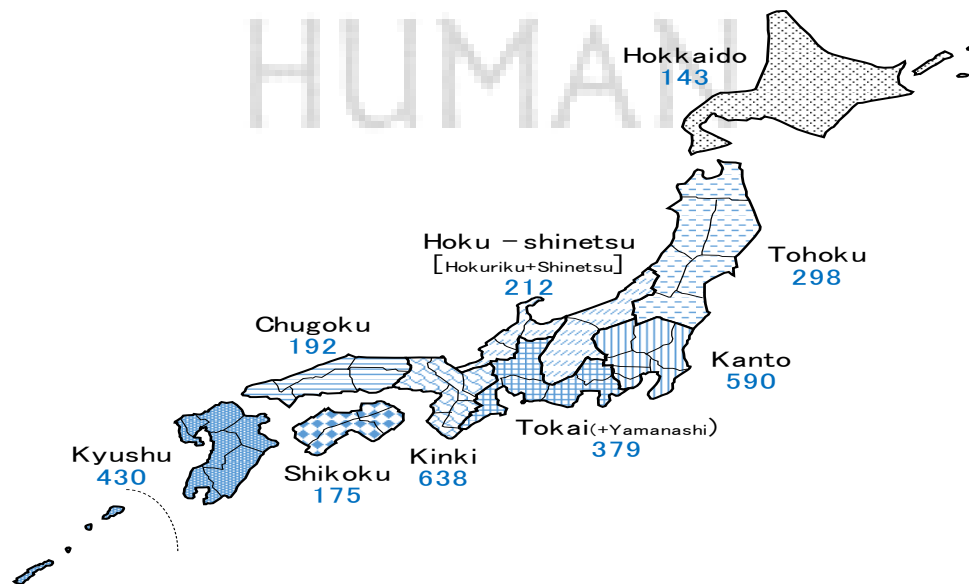


Figure 1. Distribution of valid answers

Table 2. Distribution and response to questionnaire

Area	Valid answers	(%)	6 block	4 block
Hokkaido	143	4.7	14.4	21.3
Tohoku	298	9.7		
Hoku-shinetsu	212	6.9	26.2	31.7
Kanto	590	19.3		
Tokai	379	12.4	12.4	
Kinki	638	20.9	20.9	20.9
Chugoku	192	6.3	12.0	26.1
Shikoku	175	5.7		
Kyushu	430	14.1	14.1	

Area: From north to south, Japan is subdivided into the areas shown on the map in Figure 1.

6 blocks: Japan as divided into 6 blocks, depending on common groupings considering the deflection from north to south.

4 blocks: Japan as divided into 4 blocks, depending on a broad scale considering the deflection from north to south.

Table 3. Number of returned questionnaires by prefecture

Hokkaido	143	Gumma	57	Kyoto	96	Kagawa	34
Aomori	36	Tochigi	60	Shiga	65	Kochi	59
Iwate	36	Ibaraki	52	Osaka	186	Ehime	51
Akita	48	Saitama	63	Wakayama	48	Fukuoka	131
Miyagi	81	Tokyo	155	Nara	68	Oita	53
Yamagata	39	Chiba	64	Hyogo	175	Saga	24
Fukushima	58	Kanagawa	139	Okayama	55	Nagasaki	24
Niigata	64	Yamanashi	26	Hiroshima	45	Kumamoto	61
Toyama	42	Shizuoka	69	Tottori	24	Miyazaki	47
Ishikawa	37	Aichi	129	Shimane	28	Kagoshima	55
Fukui	22	Gifu	108	Yamaguchi	40	Okinawa	35
Nagano	47	Mie	47	Tokushima	31	(unknown)	6

Table 4. Characteristics of respondents by age and sex

Age^a		
<50	281	9.2 %
50-59	557	18.1 %
60-69	1,200	39.2 %
> 69	1,018	33.2 %
Sex^b		
Female	2,824	92.2 %
Male	227	7.4 %

^a: Seven subjects did not indicate their age.

^b: Twelve subjects did not indicate their gender.

Table 5 shows characteristics of drug taking. There were no significant differences in the distribution of the number of drugs used other than anti-RA drugs in those younger than 50 years and those aged 50 to 59 years. On the other hand, significant differences in the number of drugs taken other than anti-RA drugs were noted between the younger than 50, 50-59 years, 60-69 years, and older than 69 groups ($p < 0.01$). In terms of management of drug taking, 97% of subjects answered that they managed drugs themselves, and 79.9% reported that they took drugs as prescribed.

An analysis of the effects of the number of drugs taken and adherence showed that the number of other drugs taken did not impact adherence.

Table 6 shows adherence analyzed by frequency of forgetting to take drugs. Anti-RA drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), and other drugs were reported as being missed more than 3 times a week by 4.7%, 9.8%, and 7.1% of respondents, respectively. There was a significant difference between anti-RA drugs and NSAIDs ($p < 0.05$), and between anti-RA drugs and other drugs ($P < 0.05$). Adherence with anti-RA therapy was better than that for NSAIDs and other drugs. When examined by age, adherence with anti-RA drugs and NSAIDs was significantly worse in respondents older than 70 compared with those aged 60 to 69 and those younger than 59 ($P < 0.01$). Among respondents older than 70, the number forgetting to take NSAIDs was higher than the number forgetting to take anti-RA drugs ($P < 0.01$) (Figure 2).

Similarly, in those older than 70, adherence to anti-RA drugs was better than adherence to other drugs.

Table 7 shows adherence by prefecture in Japan. The mean adherence for each drug was 84.8±4.9% for anti-RA drugs, 85.8±6.1% for NSAIDs, and 83.6±4.7% for others. Adherence rates for each drug category were above 80%.

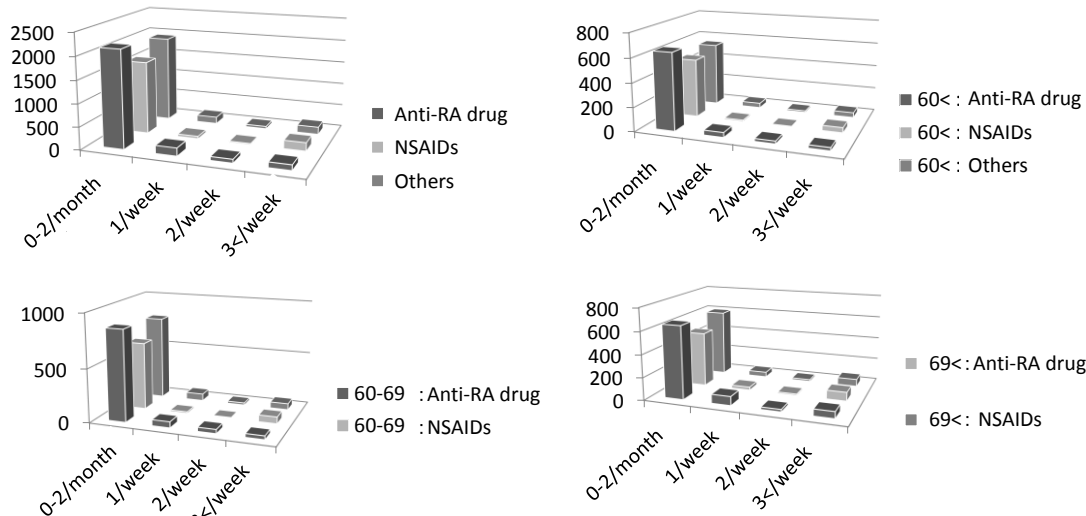
Table 8 shows the best 3 and worst 3 percentages for adherence. Adherence with anti-RA drugs ranged from 93% to 95% for the best scores and from 75% to 76% for the worst scores. There was a significant difference in adherence between the best and worst percentages in NSAIDs (P<0.01) and others (P<0.05). However there is no significant difference in anti-RA drugs.

Table 9 shows the comparison of adherence between two districts, Kanto vs Kinki, and Hokkaido vs Kyushu, each of which have large populations. There were no significant differences in adherence between these districts.

Table 5. Characteristics of drug taking

Number of drugs							
Valid answer		3,011	98.3 %				
No answer		52	1.7 %				
Number of drugs beside RA drugs		0		1-3		over 4	
(All answers)		611	20.3 %	1,521	50.5 %	879	29.2 %
< 50	[278]	86	30.9 %	135	48.6 %	57	20.5 %
50-59	[549]	146	26.6 %	286	52.1 %	117	21.3 %
60-69	[1,187]	233	19.6 %	601	50.7 %	353	29.7 %
> 69	[995]	146	14.7 %	498	50.0 %	351	35.3 %
							*
Management of drug taking							
Valid answer		3,041	99.3 %				
No answer		22	0.7 %				
Management by oneself		2,951	97.0 %				
Management by family members		75	2.5 %				
Management by institutions		15	0.5 %				
Control of amount of drugs							
Valid answer		3,012	98.3 %				
No answer		51	1.7 %				
Take drugs as prescribed				2,408	79.9 %		
Change amount of drugs depending on physical condition				604	20.1 %		

* Statistically significant difference (P < 0.05)



Y-axis: Number of forgetting to take
 Statistically significant difference in anti-RA drugs between the group <60 years and the group >69 years (P<0.01) and between the group 60-69 years and the group >69 years (P<0.01).
 Statistically significant difference in NSAIDs between the group <60 years and the group >69 years (P < 0.01) and between the group 60-69 years and the group >69 years (P < 0.01).

Figure 2. Adherence by generation

Table 6. Drug adherence

Valid answers	3,063	88.3 %
No answer	404	11.7 %

Classification of drugs	Frequency of forgetting	0-2/month	1/week	2/week	>3/week
Anti-RA drug	Valid answers 2,516	2,140 85.0 %	175 7.0 %	82 3.3 %	119 4.7 %
NSAIDs	Valid answers 1,870	1,609 86.1 %	52 2.8 %	25 1.3 %	184 9.8 %
Others	Valid answers 2,281	1,916 84.1 %	149 6.5 %	53 2.3 %	163 7.1 %

Compliance by age

Age Group	Frequency of forgetting	0-2/month	1/week	2/week	>3/week	
【<60】	Anti-RA drug	Valid answers 732	643 87.8 %	40 5.5 %	23 3.1 %	26 3.6 %
	NSAIDs	Valid answers 551	492 89.3 %	11 2.0 %	5 0.9 %	43 7.8 %
	Others	Valid answers 632	539 85.2 %	39 6.2 %	13 2.1 %	41 6.5 %
	Frequency of forgetting	0-2/month	1/week	2/week	>3/week	
【60-69】	Anti-RA drug	Valid answers 980	852 86.9 %	56 5.7 %	38 3.9 %	34 3.5 %
	NSAIDs	Valid answers 718	633 88.2 %	14 1.9 %	8 1.1 %	63 8.8 %
	Others	Valid answers 930	787 84.6 %	65 7.0 %	20 2.2 %	58 6.2 %
	Frequency of forgetting	0-2/month	1/week	2/week	>3/week	
【>69】	Anti-RA drug	Valid answers 804	645 80.3 %	79 9.8 %	21 2.6 %	59 7.3 %
	NSAIDs	Valid answers 601	484 80.5 %	27 4.5 %	12 2.0 %	78 13.0 %
	Others	Valid answers 719	595 82.8 %	44 6.1 %	16 2.2 %	64 8.9 %
	Frequency of forgetting	0-2/month	1/week	2/week	>3/week	

* Statistically significant difference (P < 0.05)

Table 7. Adherence by prefectures

Rate of no or low non-adherence (0-2 times/month) %
A : Anti-RA, B : NSAIDs C : Others

	A	B	C		A	B	C		A	B	C		A	B	C
Hokkaido	83.2	86.6	85.9	Gumma	86.7	83.9	82.9	Kyoto	77.6	79.2	70.4	Kagawa	80.8	87.0	88.0
Aomori	77.4	73.3	88.5	Tochigi	84.8	85.0	77.3	Shiga	87.3	79.5	80.4	Kochi	86.0	79.5	82.2
Iwate	90.0	88.5	81.5	Ibaraki	89.7	86.7	83.8	Osaka	88.8	87.8	83.3	Ehime	88.6	83.3	81.6
Akita	85.7	75.0	81.8	Saitama	84.9	88.2	81.4	Wakayama	82.9	75.8	77.8	Fukuoka	84.4	82.4	86.7
Miyagi	81.8	92.7	82.8	Tokyo	91.5	90.6	85.9	Nara	78.7	77.4	82.7	Osaka	88.8	87.8	83.3
Yamagata	84.3	83.3	78.6	Chiba	84.6	82.1	80.8	Hyogo	87.8	89.2	87.8	Saga	76.2	76.5	81.3
Fukushima	85.4	94.3	90.5	Kanagawa	85.4	85.9	84.7	Okayama	93.3	94.6	88.6	Nagasaki	77.3	100.0	82.4
Niigata	83.6	85.4	84.4	Yamanashi	80.0	81.3	85.7	Hiroshima	91.7	87.0	87.1	Kumamoto	88.7	91.9	87.5
Toyama	81.3	80.8	87.1	Shizuoka	79.3	82.1	78.3	Tottori	84.2	81.8	84.2	Miyazaki	88.9	96.2	81.1
Ishikawa	92.6	90.5	86.2	Aichi	83.9	86.7	89.0	Shimane	95.0	81.3	85.7	Kagoshima	85.4	90.2	86.7
Fukui	75.0	85.7	75.0	Gifu	79.3	87.7	86.3	Yamaguchi	86.2	82.6	73.1	Okinawa	90.0	91.3	95.7
Nagano	86.5	91.7	76.9	Mie	75.6	90.9	88.2	Tokushima	92.3	100.0	87.0				

Table 8. Best and worst percentages of adherence

	Best 3 Prefectures			Worst 3 Prefectures		
	1	2	3	45	46	47
Anti-RA drugs	95%	93%	93%	76%	76%	75%
NSAIDs **	100%	100%	96%	76%	75%	73%
Others *	96%	91%	89%	75%	73%	70%

* Statistically significant difference between the best 3 prefectures and the worst 3 prefectures (P < 0.05)

** Statistically significant difference between the best 3 prefectures and the worst 3 prefectures (P < 0.01)

Table 9. Adherence comparison between two districts

		Kanto [4]		vs.		Kinki [6]			
【Kanto】	Frequency of forgetting		0-2/month		1/week		2/week		>3/week
Anti-RA drug	Valid answers	482	421 87.4 %		31 6.4 %		11 2.3 %		19 3.9 %
NSAIDs	Valid answers	362	314 86.7 %		10 2.8 %		3 0.8 %		35 9.7 %
Others	Valid answers	450	375 83.4 %		32 7.1 %		11 2.4 %		32 7.1 %
【Kinki】	Frequency of forgetting		0-2/month		1/week		2/week		>3/week
Anti RA drug	Valid answers	527	448 85.0 %		33 6.3 %		18 3.4 %		28 5.3 %
NSAIDs	Valid answers	378	318 84.1 %		13 3.4 %		3 0.9 %		44 11.6 %
Others	Valid answers	479	392 81.8 %		34 7.1 %		13 2.7 %		40 8.4 %

		Hokkaido [1]		vs.		Kyushu [9]			
【Hokkaido】	Frequency of forgetting		0-2/month		1/week		2/week		>3/week
Anti-RA drug	Valid answers	125	104 83.2 %		7 5.6 %		6 4.8 %		8 6.4 %
NSAIDs	Valid answers	105	91 86.6 %		1 1.0 %		1 1.0 %		12 11.4 %
Others	Valid answers	106	91 85.9 %		5 4.7 %		3 2.8 %		7 6.6 %
【Kyushu】	Frequency of forgetting		0-2/month		1/week		2/week		>3/week
Anti-RA drug	Valid answers	356	303 85.1 %		29 8.1 %		13 3.7 %		11 3.1 %
NSAIDs	Valid answers	283	247 87.3 %		11 3.9 %		6 2.1 %		19 6.7 %
Others	Valid answers	336	290 86.3 %		22 6.5 %		6 1.8 %		18 5.4 %

DISCUSSION

Drug therapy is essential for every patient with RA, although doctors and pharmacists often find it difficult to identify adherence to therapy in a clinical setting (16). With drugs like methotrexate (MTX), adherence to therapy not only impacts the efficacy of treatment but also the appearance of severe side effects when too much MTX is prescribed (17,18). In addition, because planning regarding the next drug to be tried is made based on results of previous data, including physical and laboratory findings, understanding adherence to therapy is critical to choosing the appropriate therapy for each patient. Without adherence, chronic diseases like RA cannot be treated successfully (19, 20). We performed an epidemiological survey to identify basic adherence with drug therapies and any difficulties in taking medication among patients with RA in Japan. We adjusted the number of questionnaires sent to each district based on the district size (21) to avoid introducing a biased response by district.

The distribution rate by age was similar to that of a previous study, in which the highest number of respondents was aged 60 to 69 (20). Based on data from a previous study, most patients in Japan are diagnosed with RA in their 40s, although good access to therapy means that patients tend to survive until they are elderly (21). It is important to recognize that better treatment leads to an increase in aged patients, who need careful treatment, as they likely suffer from multiple disorders (22). Because the elderly have more disorders that require drug therapy than younger patients, physicians must consider the need for multiple types of therapy when treating these patients (21, 25).

In terms of gender, 92.2% subjects in this study were female, a rate that is higher than that of previous reports (23, 24). This could be because the number of patients with RA is higher in women than in men, and that women are more interested in their disease and prefer to communicate with other patients using patients' association and social media. However, there were no gender differences in adherence.

Our findings also showed that there was no significant relationship between the number of drugs used and adherence. This means that even patients taking only one drug may skip doses. Thus, physicians must consider patients' adherence based on lifestyle, age, and mental status (26-28).

Almost all patients, including the elderly, managed their drugs themselves and reported taking drugs as prescribed. This finding indicates that even aged patients tend to be independent in terms of their drug therapy. However, in a previous study, patients were shown to misuse and skip drugs, even with a simple prescription. Thus additional ways of studying adherence are needed in future studies (29).

There was a significant difference between anti-RA drugs and NSAIDs, and anti-RA drugs and other drugs for forgetting to take drugs, with fewer respondents, reporting and missing anti-RA treatments. This finding suggests that patients with RA pay closer attention to take anti-RA drugs than other drugs. Because disease education is often provided at the start of RA therapy, it is possible that patients with RA have a better understanding of the importance of adhering to therapy (30,31).

This study found that adherence all over Japan is uniform, with no prefecture reporting less than 70% adherence. This adherence rate is better than rates in previous studies (1-3, 32), which ranged from around 50% to 60%.

Although there was a significant difference in adherence between best and worst scores in all drug categories, there was not enough data to assess these differences. It is possible that other factors, such as access to appropriate specialists and institutions may impact these scores. There was no significant difference in adherence between Kanto vs Kinki, and Hokkaido vs Kyushu, each of which has a large population.

CONCLUSION

We surveyed the actual adherence to drug therapy in patients with RA in Japan. Our findings regarding patients' adherence were better than previous reports. This may be related to information and disease education provided when patients are diagnosed with RA in Japan. When assessing future drug therapies, data on adherence may be a key factor in terms of providing both effective and cost-effective therapy for patient with RA.

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Conflict of interest: None

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