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## Study of Drug Adherence in a Large Japanese Population with Rheumatoid Arthritis: An Epidemiological Survey Focused on Patient Backgrounds

	
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### ABSTRACT

Objective: Appropriate adherence is essential for drug therapy to be effective in patients with rheumatoid arthritis (RA). However, data on drug adherence in Japan is limited. Identifying real situations regarding adherence and factors that affect it can help in the choice of therapy for patients with RA. We studied adherence and related factors in patients with RA in Japan. Methods: We conducted a questionnaire 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 to 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. Results showed that 62.6% of patients use some sort of method to help them remember to take their medication. Overall, 51% of patients experienced difficulty opening or removing drugs from their packages. There were no significant differences in adherence rates between patients using helpful methods compared with those not using helpful methods, except for NSAID use (>3 weeks). Based on open comments, 41% of subjects experienced problems with adherence. Furthermore, many comments were related to the drug package and patients' hopes for packaging that was easier to use. Conclusion: Because patients with RA are living longer, it is important to track drug adherence. Understanding true rates of adherence and problems that impact it may help in choosing the most appropriate drug for patients and encourage adherence.

## INTRODUCTION

Pharmaceutical options for rheumatoid arthritis (RA) have grown in both number and quality [1-3]. Because effective drug therapy is the priority for every patient with RA, appropriate use of therapies is essential. However, it is difficult to assess drug efficacy without also examining adherence with therapy. Previous studies of adherence among patients with chronic diseases showed that only 50–60% of patients take medicine as directed [4-11]. Because RA therapy includes both anti-immune and biological drugs, poor adherence results in not only lack of effectiveness but also a waste of money, as these drugs are expensive [7, 8]. From an economic point of view, poor adherence after a patient fills a prescription leads to increased medical insurance expenses and patients' out-of-pocket costs. In Japan, where the number of elderly patients is increasing, patients tend to receive multiple medical checkups and take multiple drugs; poor adherence and missed doses can induce secondary effects [12]. Considering the large number of choices for the treatment of RA, it is important to use drugs that are not only effective but those that patients also have a personal preference for. If we hope to see better therapeutic outcomes in patients with RA, we need to know their true adherence to therapy and what factors impact this adherence so that the most appropriate therapeutic option can be chosen.

The aim of this study was to estimate actual drug adherence among patients with RA. To obtain unbiased data from all over Japan, we used a simple questionnaire survey that was distributed with the cooperation of a Japanese RA patients' association.

Because our previous report of this survey showed that adherence depended on the area surveyed and the age of the population [13], this study focused on patient backgrounds and situations regarding taking their medication as directed.

## MATERIALS AND METHODS

### Subjects

In November 2012, the Japanese RA patients' association (JRPA; in Japanese 'Ryumachitomonokai') agreed to assist with the explanation of the aim and performance of the study. In December 2012, we sent simple questionnaires printed on pre-paid post-cards to 5000 randomly selected subjects (from the list of JRPA) in all prefectures in Japan, considering a balanced distribution of patients in each prefecture. Every post-card was included in an envelope from the JRPA containing a letter of explanation indicating that return of the questionnaire represented providing informed consent.

### Questionnaire

The beginning of the questionnaire explained that we were gathering information on drug adherence, the types of drugs used, and any difficulties in using them. The questionnaire included 10 items, some of which allowed us to assess the relation between patient backgrounds and drug adherence. In addition, we provided space for open comments (Table 1).

## Statistical analysis

Statistical analysis was performed using SPSS (IBM) software version 17.0 for Windows. Inter-group analysis was performed using Student's *t*-test. *P* values less than 0.05 were considered significant.

## RESULTS

Figure 1 shows the distribution and number of questionnaires we received. The overall response rate was 69.3% (3467/5000); after removal of questionnaires with invalid answers, 3063 of the returned questionnaires (88.3%) were assessed.

Table 2 shows subject characteristics in terms of age and sex. Subjects younger than 50 years accounted for 9.2% of responses, 50–59 years for 18.1%, 60–69 years for 39.2%, and older than 69 years for 33.2%. In terms of sex, 92.2% of valid answers were from women and 7.4% were from males; the remainder did not indicate sex.

Table 3 shows the methods that subjects used to help them adhere to drug regimens; 62.6% of patients used some helpful method to remind them to take their medication. The most common method was to divide pills and store them in a container (43.8%), followed by using some type of calendar (9.2%), and other methods (8.8%). There were some patients who used two methods jointly. In the open comments, subjects reported many methods to avoid missing their medication.

Table 4 shows the experiences of difficulty opening and taking drugs from their packages. Among the valid answers, 51% of patients experienced difficulty opening drug packages. Problems with pills and capsules were reported by 42%, problems with suppositories by 11.2%, problems with powder by 9.8%, and problems with other types of medications by 1.8%. Subjects were permitted to choose multiple responses.

Table 5 shows the comparison of adherence between patients using some method to help with adherence and those not using any methods to help. There were no significant differences in adherence between those using methods to help and those not using methods to help except for NSAID use (>3 weeks).

Tables 6 and 7 show open responses listed on the questionnaires. Among all comments, 41% mentioned concerns about taking the drug, including skipping or missing a dose, the drug name, and the number of drugs being taken. A total of 14% provided detail information regarding how they prevented skipping or missing doses. A total of 10% described difficulty opening packages and patients' hopes for packaging that was easier to use. Five percent reported wanting better usability, such as drugs that were easier to swallow or identify, or that had a better shape. In addition, 5% mentioned the reality of self-management of drugs and their desire for some ideal system to help them manage their medications. Adherence-related concerns were addressed in 56% of the comments and difficulties with drug-related use were addressed in 20% of the comments. In addition, 42% of comments were related to pills and capsules, which are commonly used drug forms in Japan.

Table 7 shows the analysis of free comments and opinions. Information on drug name, skipped doses, prevention of missed doses, and problems with opening the packaging appeared commonly in the comments. Subjects also expressed hope that drugs would be easier to swallow and identify.

## DISCUSSION

In the previous report of this survey, we showed adherence with therapy among patients with RA was more than 75% for every drug, including anti-RA agents, NSAIDs, and others [13]. This rate is higher than previous reports [4, 5]. This higher rate may be partly due to the fact that members of JRPA have good access to information about their disease and drugs used to treat it, and they tend to make efforts to take their medications regularly. Since valid answers were received from all areas in Japan, there was no bias in terms of location of responders.

Most subjects in the current study (72.4%) were older than 60 years. Thus, the comments expressed by subjects in this study reflect the reality of medication use in elderly patients. It is also accepted that assessing patient adherence reflects an assessment of patient backgrounds and that most patients in this study were elderly. Table 3 shows that 43.8% of patients divide and store medication in a container by themselves and 9.2% use calendar-type devices. Others (8.8%) come up with their own methods to increase adherence. The relatively good adherence results in this study are considered to be a function of the users' own efforts regarding taking their medication. These subjects indicated that they have a high focus on ensuring that they adhere to their medication regimens, and many of the open comments detailed their daily struggles. However, the results showed that even with the application of key methods, patients still sometimes miss a dose. This finding suggests that some patients are unable to adhere to their medication recommendations despite the different ways in which they try to do so [14, 15]. As 51.0% of patients experienced difficulty in opening drug packages, it seems that easy-open packages may be one way to address some of the problems with everyday drug use. Opening the packages of commonly used drug forms, such as pills and capsules, was mentioned by 42% of subjects; thus this represents a serious issue in the treatment and management of RA. This issue is closely related to the need for a universal design for drug packaging and other medical devices that patients use. [16, 17]. In the adherence comparison, there were no significant differences between patients using some method to help them remember their medication and those not using any methods (except for NSAIDs, for which patients tend to manage dosing on their own depending on pain levels). However, even among patients making efforts not to miss drug doses, about 15% of patients reported missing anti-RA therapy. This could be important information for physicians to use to open a conversation regarding drug adherence with patients. In addition, if patients do not use any methods to increase adherence themselves, adherence may become worse.

There were 1236 (36.3%) comments and opinions, indicating that more than one third of patients provided comments, 41% of which were related to the situation of drug taking and 14% of which described the methods that patients used to prevent missing doses. It appears that many patients already do what they are able to do to help increase their medication adherence. These comments also suggest that patients with chronic diseases, like RA, recognize the importance of adhering to drug therapy. Thus, doctors and other medical personnel should pay attention to adherence and be ready to offer a plan to help patients remember to take their medication [18].

Assuming that drug therapy is essential for every RA patient, there were a surprising number of comments regarding drugs and their use. Among these comments, items related to information about drugs were most common, followed by items related to adherence. In addition, subjects indicated a desire for information regarding how to prevent missing doses. This finding suggests that patients are concerned about appropriate drug information and use. Many patients described their own ways of avoiding missed doses, and it is important to recognize these efforts. Some patients not only used an ordinary container, but also made their own devices, in addition to trying to place the medication where they would definitely see it. A partner of one elderly patient with dementia put a weeks' worth of drugs into a self-made container for the patient and removed drugs from the container every time a dose was needed. These actual reports indicate that maintaining adherence among elderly patients involves a lot of hard work [19, 20]. However, there are few opportunities to assess medication use in a community, so it is necessary for healthcare providers to review the appropriateness of each situation and the efficacy of any methods being implemented by patients [21-23]. Understanding the realities of medication use, including adherence and any difficulties experienced during medication use, could help in the development of support programs and innovative adherence programs, such as those including new devices or integrated information systems. For some patients with RA, handling drugs and devices may be difficult, and actual information from these types of situations would be helpful [18].

Because patient age is increasing continuously worldwide, if we hope to ensure better adherence, we should recognize the reality faced by patients in a community setting [24-28]. Integrated support and monitoring are necessary for good results of drug therapy as well as cost-effectiveness.

## **CONCLUSION**

From the results of this survey, it appears that patients with RA already make several efforts to increase their own drug adherence. We need to recognize the current adherence rate and the associated patient backgrounds. Based on these findings, patient support plans along with innovative ideas and tools are needed to help improve patient adherence with drug therapy. For patients with RA, some type of universal design in medication packaging may improve medication use.

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## **Conflict of interest**

None

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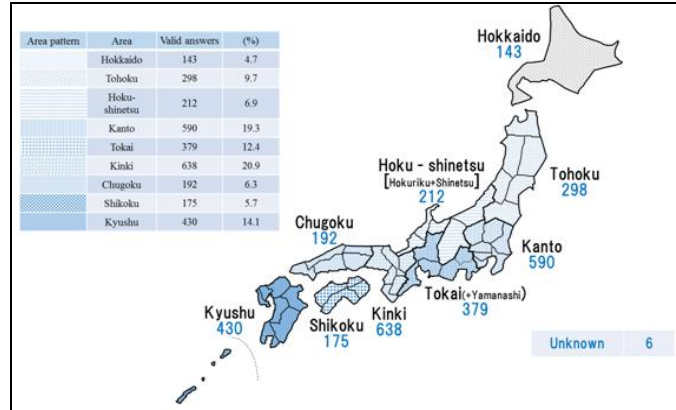
**Table 1. Questionnaire**

Please select the most appropriate responses below (✓, /, O)

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 other than drugs for rheumatoid arthritis (RA)
  1. None 2. 1-3 3. More than 4
5. Frequency of non-adherence (forgetting to take drugs)

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

6. Quantity of drug intake
  1. Take drugs according to prescription 2. Change amount of drugs depending on physical condition
7. Method of reminding to avoid missing a dose
  1. None 2. Subdivide. Keep container 3. Use calendar-type container 4. Other
8. Have you experienced difficulty opening (using) drug packages? [Select multiple items as appropriate]
  1. None 2. Pill, Capsule 3. Powder, Granule 4. Suppository 5. Other
9. Your prefecture:
10. Open comments:



**Fig. 1. Distribution and response number of the questionnaire.**

**Table 2. Subject characteristics**

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

<sup>a</sup> 7 subjects did not indicate age.  
<sup>b</sup> 12 subjects did not indicate gender.

**Table 3. Methods patients used to help adhere to drug therapy**

**Methods for remembering to take prescribed drugs**

Valid answer	2,988	97.6%
No answer	75	2.4%
1. No helpful ideas	1,118	37.4%
2. Divide and store in container	1,310	43.8%
3. Use calendar-type container	274	9.2%
4. Ideas 2 and 3	12	0.4%
5. Other	262	8.8%
6. Ideas 2 and 5	11	0.4%

**Other methods to help with adherence to drug therapy: Open responses**

- Making a drug calendar
- Placing drugs on the dining table so as not to forget
- Preparing water so as not to forget to take drug after a meal
- Noting the drugs taken each day and storing them separately
- Placing drugs for partner with dementia before taking them
- Preparing the next day's drugs on the previous night

**Table 4. Experience difficulty opening and taking drugs from the package - Opening status of drug packages**

Response rate			
Valid answer	3,326	95.9%	
No answer	141	4.1%	
Responses			
No	1,630	49.0%	
Yes	1,696	51.0%	
Type			
Pill/capsule	1,396	42.0%	[Multiple responses allowed]
Powder	327	9.8%	
Suppository	371	11.2%	
Others	60	1.8%	

**Table 5. Comparison of adherence between patients using methods to help with adherence and those not using any methods to help with adherence**

No methods	Forget to take	0-2/month	1/week	2/week	>3/week	
Anti-RA	913	764 <b>83.7%</b>	77 8.4%	28 3.1%	44 4.8%	* }
NSAIDs	634	535 <b>84.4%</b>	17 2.7%	6 0.9%	76 12.0%	
Others	780	657 <b>84.3%</b>	47 6.0%	14 1.8%	62 7.9%	
Using methods						
Anti-RA	1,603	1,376 <b>85.7%</b>	98 6.1%	54 3.4%	75 4.8%	
NSAIDs	1,236	1,074 <b>87.0%</b>	35 2.8%	19 1.5%	108 8.7%	
Others	1,501	1,259 <b>83.9%</b>	102 6.8%	39 2.6%	101 6.7%	

\* Statistically significant difference (P<0.05)

**Table 6. Classification of open comments and opinions**

**Number of comments and opinions related to adherence among all comments**  
(comments related to adherence/overall comments =1250/3440 36.3%)

\* Omitting 16 comments and opinions that related patients' associations matters which had no relation of survey

Contents of comments and opinions	n	%
A Situation of drug taking; skipping/missing dose, drug name, number of drugs	510	41%
B Details of preventing skipping/missing dose	174	14%
C Reality of easier drug taking and hopes regarding drug costs	100	8%
D Reality of difficulty of opening packages and hopes for easier-to-open drug packages	126	10%
E Hopes for better usability (swallowing, use, identification, shape)	61	5%
F Reality of self management of drugs	61	5%
G Status of RA, history of treatment, future anxiety, insufficiency of drugs	308	25%

**Table 7. Analysis of open comments and opinions**

Item of comments	Detail of comments	Additional information
A Information of drug name (268)	Expanding the use of biologics Methotrexate and other anti-RA drugs	1. Etanercept, 2. Tocilizumab, 3. Infliximab 4. Adalimumab, 5. Abatacept, 6. Golimumab
	Other information of drug use (name, frequency, amount)	Comments that patients take plenty of drugs ; 24 different drugs (2)
B Skipping/missing doses (169)	Situation of skipping/missing doses	Skipped/missed doses (87)
	Reasons for skipping/missing doses	No skipped/no missed doses (82)
B Prevention of missing dose (174)	Methods to prevent missing doses (eg. One Dose Package, note, setting on the table, etc.)	Use of a reminder (11)
C Cost of drugs (100)	Difficulty of affording very expensive drugs, and some hope to eventually take them	Somebody inevitably stops taking drug
D Opening packages (111)	Examples of drugs that are hard to open, how to open drugs, and reality of difficulty when RA activity is high	Difficulty removing drugs from packaging
E Hope for drugs (61)	Easy to swallow (smaller pill is better)↔Easy to handle (larger pill is better) Hope for better identification (Eg. use katakana characters or colors for identification.)	Hope for oral administration rather than injection Hope for painless injection
F Self-management of drugs (61)	When patients have pain or changes in their physical condition, they tend to alter the dosage when self-managing their drugs	Catching a cold requires self-management of drugs
	NSAIDs, anti-RA drugs, immune suppressants, vitamins	Sulfasalazine, Tacrolimus hydrate, Folic acid
G Self-condition of RA (308)	Doctor allows patient to self-manage drugs	12 cases
	History of disease, anxiety toward the future, no satisfaction, and hope for medical care	Hope for low-priced bio-similar drugs