

# Effect of patient education on medication adherence of patients with rheumatoid arthritis: a randomized controlled trial

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**Purpose:** There is a general understanding that patient educational interventions for enhancing medication adherence are important. However, their success at improving adherence is debatable. This study aimed to assess the influence of different modes of patient education on medication adherence in patients with rheumatoid arthritis (RA).

**Materials and methods:** One hundred and twenty RA patients with non-adherence, defined as pill count  $\leq 80\%$  or medication-taking behavior questionnaire for Thai patient  $\leq 23$ , were randomized by block randomization and assigned in a 1:1 allocation ratio to two study arms: multi-component intervention group or single intervention group. The multi-component intervention group received 30-minute directed counseling and a disease information pamphlet. The single intervention group received only a disease information pamphlet. The primary outcomes were an improvement in an adherence rate measured by pill count after 12 weeks. The Thai Clinical Trial Registry number is TCTR20171207003.

**Results:** After 12 weeks, the pill count adherence rate increased significantly from baseline in both study groups. In the multi-component intervention group, adherence rate increased from  $92.21 \pm 14.05$  to  $97.59 \pm 10.07$  ( $P=0.002$ ) and in the single intervention group, it increased from  $88.60 \pm 19.66$  to  $92.42 \pm 14.27$  ( $P=0.044$ ). However, the mean difference between the multi-component intervention group and the single intervention group was not significant ( $5.38 \pm 12.90$  vs  $3.18 \pm 14.23$ ,  $P=0.531$ ). Clinical outcomes, including disease activity score 28, EuroQoL-5D, EuroQol visual analog scale, pain score, and physician global assessment were unchanged from baseline in both groups.

**Conclusion:** Patient education significantly improved adherence. However, there were no differences between single education intervention and multi-component education intervention in improving medication adherence. Provision of a disease information pamphlet with or without directed counseling can equally enhance medication adherence of patients with RA.

**Keywords:** adherence, rheumatoid arthritis, education, disease pamphlet

## Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory condition, affecting from 0.5% to 1% of the general population worldwide. The precise causes remain uncertain. A variety of genetic, hormonal, environmental, and infectious agents may contribute to susceptibility and pathogenesis. Inadequately controlled RA leads to serious joint damage, functional disability, morbidity, reduced health-related quality of life, and mortality, which cause a vast economic burden.<sup>1,2</sup>

Prevalence of RA in Thailand is 0.12%.<sup>3</sup> Chronic rheumatic diseases have a substantial negative effect on both the health and quality of life of patients and their

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caregivers. Moreover, these chronic diseases also have a great influence on society, in terms of health resource utilization, work productivity loss, disability, and death.<sup>4</sup> In 2007, the average societal cost of RA in Thailand was 41.1% of a patient's average annual income, of which, 79.6% accounted for the direct cost of treatment.<sup>5</sup>

Over the last decade, significant developments have been made in the therapy of RA with the occurrence of novel biological therapies. Several studies have shown that timelier and more aggressive therapy with conventional and biological disease-modifying anti-rheumatic drugs (DMARDs) reduces arthritis symptoms and slows disease progression. However, DMARDs adherence rate in patients with RA is very low, and has varied from 16.4% to 76.9%.<sup>6–11</sup> The non-adherence results in higher disease activity, radiographic damage, disability, a lower quality of life, and a higher health care cost.<sup>12–14</sup> Multiple factors have been shown to affect medication adherence in patients with RA. However, there are diverging results about the influences of patient and disease characteristics on adherence.<sup>7,11,15–33</sup>

A number of intervention trials have been performed to improve adherence to medication.<sup>9,34–42</sup> These intervention approaches can be categorized into four groups: educational, behavioral, cognitive behavioral, and multi-component interventions.<sup>43</sup> Recently, a systematic review determined the impact of different interventions on medication adherence and found that multicomponent interventions had the greatest evidence for improving adherence.<sup>36,44</sup> However, their effectiveness at enhancing adherence is still uncertain. The National Institute for Health and Care Excellence guideline in 2009 recommended considering any intervention to improve adherence on an individual basis and to modify the intervention to the actual needs of the patients.<sup>45</sup>

This study aimed to assess the impact of different modes of patient education on medication adherence in Thai RA patients.

## Materials and methods

### Participants

Patients who fulfilled the 2010 American College of Rheumatology/European League against Rheumatism criteria for RA were recruited from rheumatology clinic of the Phramongkutklao Hospital from March 2017 to February 2018. Patients were excluded if they were <18 years of age, diagnosed with life-threatening conditions, unable to read Thai, unable to take medication by him/herself, had a high disease activity (disease activity score-28, [DAS28] >5.1), or had a severe mental disorder.

## Methods

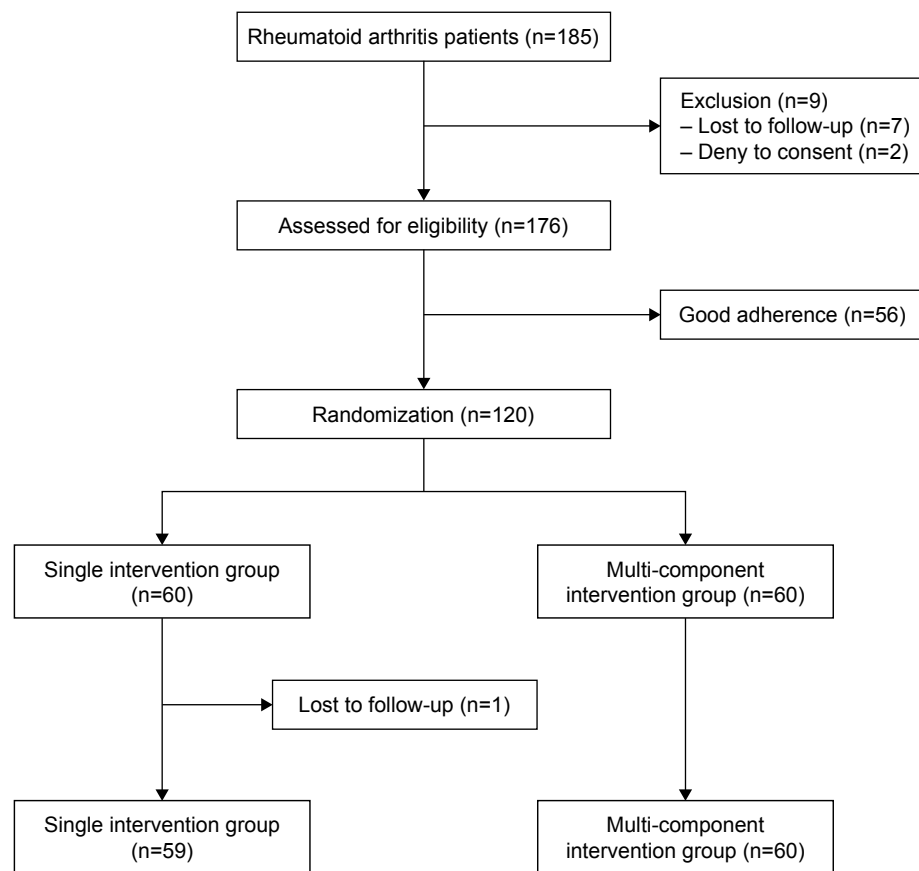
A total of 185 patients with RA were enrolled. Fifty-six patients with good adherence, defined as medication-taking behavior (MTB) questionnaire for the Thai patient >23 or pill count >80%, were excluded. Seven patients could not follow the study protocol and two denied participating. One hundred and twenty patients with non-adherence were randomized by block randomization and allocated in a 1:1 allocation ratio to two study arms: multi-component intervention group or single intervention group. The multi-component intervention group received a 30-minute directed counseling and a disease information pamphlet. The information pamphlet provided brief information on RA disease and drugs commonly used to treat RA, including usage and dosage information. The single intervention group received only a disease information pamphlet. The study flow chart was depicted in Figure 1.

Baseline demographic and disease characteristics included age, sex, marital status, occupation, salary, year of education, medical insurance, disease duration, tobacco use, alcohol use, comorbidity, rheumatoid factor, anti-citrullinated peptide antibody, dosage and number of DMARDs, and the total number of medicines. All patients were asked to finish a set of standardized self-reporting questionnaires (MTB), patient global assessment (PGA), pain score, EuroQoL-5D (EQ-5D), hospital anxiety and depression scale (HADS), brief illness perception questionnaire (B-IPQ), Montreal cognitive assessment (MoCA), and Thai mental status examination (TMSE). The individual medication was retrieved by querying the electronic medical records combined with patients' self-report. DAS28 and physician global assessment (PhGA) were assessed by blinded rheumatologists. After 12 weeks, patients completed a second set of questionnaires (MTB, PGA, pain score, EQ-5D, HADS, and B-IPQ) and were assessed by the same blinded rheumatologist. One patient in the single intervention group was lost to follow-up.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and adhered to the principles outlined in the Guideline for Good Clinical Practice International Conference on Harmonization Tripartite Guideline (January 1997). The study protocol was approved by the institutional review board of the Royal Thai army medical department. Written informed consent was obtained from each patient. The Thai Clinical Trial Registry number is TCTR20171207003.

### Pill count adherence rate

This objective measure counts the number of drugs that have been taken between two visits. This number would then be



**Figure 1** Patient flow chart.

compared with the total number of drugs received by the patient to calculate the actual adherence rate. ([Number of dosage units dispensed – number of dosage units which remained]/[prescribed number of dosage unit per day × number of days between two visits]). This study categorized adherence as follows: patients with adherence rates >80% were considered to be good adherents to the medication, and those with adherence rates ≤80% were considered to be non-adherents to the medication.

### Self-reported adherence

Adherence was also assessed by using the MTB score. This score has been developed and validated in 1,156 Thai patients. It has clearer and more specific language, lower number of items, and better reliability and validity than the Thai version of the 8-item Morisky Medication Adherence Scale (MMAS) to measure medication adherence of the Thai patients. The MTB-Thai consisted of 6 items (forget to take medicines, not taking medicines at times prescribed, stop taking medicines because of adverse drug reactions, stop taking medicines because of getting better, stop taking medicines for other reasons, and adjust dosage regimens)

of which, recall periods were 2 weeks. The highest score was 24. Scores <22 represent “low adherence”, 22–23 suggest “medium adherence”, and equal to 24 indicate “high adherence”.<sup>46</sup>

### Quality of life

The general health status of each patient was determined using the EQ-5D-5L. The EQ-5D-5L consists of 2 scales; the EQ-5D-5L descriptive system and the EQ visual analog scale (EQ-VAS). The descriptive system comprises five dimensions and each dimension has five levels. The EQ-VAS records the patient's health on a 20 cm vertical VAS.<sup>47</sup>

### Disease activity

Disease activity was assessed by using DAS28, incorporating 28 swollen and tender joint counts, patient's global health assessment on a 100 mm VAS, and erythrocyte sedimentation rate (mm/hour).<sup>48</sup>

### Anxiety and depression

The HADS was used to measure both anxiety and depression. Each subscale contains seven items, which are rated

on a 4-point scale and scored from 0 to 3 with total scores varying from 0 to 21 for each subscale. Scores between 8 and 10 suggest a “possible case”; and 11 and 21 designate a “probable case of anxiety/depression”. These cutoff points have been found to have sensitivity and specificity of 0.8.<sup>49,50</sup>

## Illness perception

The B-IPQ was utilized to evaluate patients’ perceptions of their disease. It comprises 8 items with each level scored from 0 to 10. Five items measure cognitive illness representations: consequences, identity, personal control, timeline, and treatment control; two items gauge emotional representations: concern and emotional responses; and one item assesses illness comprehensibility.<sup>51,52</sup>

## Cognitive assessment

The Thai version of the MoCA-T test is a translated neuropsychiatric test for measuring the mental status of Thai patients. The MoCA-T measures several cognitive domains, including attention, concentration, executive functions, language, orientation to time and place, short-term memory recall task, visuospatial abilities, and working memory. Education attainment was a significant factor correlated with the score of MoCA-T. The compensation by adding one point for subjects with year of education  $\leq 6$  was more appropriate in Thai subjects. The score  $\leq 24$  of MoCA-T showed the sensitivity and specificity of 0.8.<sup>53</sup>

The TMSE is another neuropsychiatric test developed for Thais. It consists of six subtests concerning attention, calculation, language, orientation, recall, and registration. The cutoff point for the diagnosis of healthy Thai elderly for TMSE is  $>23$  points. This test is sensitive, reliable, and is an applicable mental status examination for Thai subjects who have various socioeconomic status as well as various levels of education and traditional status.<sup>54</sup>

## Outcome measures

The primary endpoints were differences in adherence rates, measured by pill count and MTB after 12 weeks between multi-component intervention group and single intervention group. The secondary endpoints were the changes in RA disease activity as measured by DAS28, pain score, and PhGA by VAS, EQ-5D-5L questionnaire, Thai-HADS questionnaire, and B-IPQ after 12 weeks between multi-component intervention group and single intervention group.

## Sample size calculation

The increase in patient’s adherence to treatment was expected to increase from 55% to 85%. A sample size calculation revealed that a sample of 47 patients in each group was

enough to elucidate such difference at 0.05 alpha error and 0.90 power of the test. Sample size calculation was performed using the n4Studies program.<sup>55</sup>

## Statistical analyses

Data were described by standard descriptive statistics. Absolute and relative frequencies were used for categorical variables. Continuous variables were described by mean and range. Randomization was checked by chi-squared test or Fisher’s exact test for categorical variables and independent Student’s *t*-test for continuous variables. The analysis described was based on an intention-to-treat approach. Significant level was set at  $P < 0.05$ . All statistical analyses were performed with IBM SPSS Statistics for version 23.

## Results

### Demographic measures

Patient allocation was well balanced. Baseline age, education, income, and underlying disease were not different between the multi-component intervention group and single intervention group (Table 1). The mean age in the multi-component intervention group was  $55.82 \pm 11.25$  years, whereas it was  $57.20 \pm 12.24$  years in the single intervention group. Females were 83.1% in the multi-component intervention group, whereas they were 85% in the single intervention group. There were no differences in disease duration, duration of treatment, extra-articular manifestations, the presence of autoantibodies, disease activity, number of medications, quality of life, illness perception, or cognitive and mental status between the multi-component intervention group and single intervention group. Percentage of patients with anxiety was greater in multi-component intervention group than in single intervention group (10% vs 0%,  $P = 0.027$ ). The mean disease duration in the multi-component intervention group was  $8.29 \pm 7.91$  years, whereas it was  $7.73 \pm 6.93$  years in the single intervention group. Baseline pill count adherence rates ( $92.21 \pm 14.05$  vs  $88.60 \pm 19.66$ ,  $P = 0.251$ ) and MTB-Thai scores ( $21.68 \pm 1.91$  vs  $21.61 \pm 2.67$ ,  $P = 0.863$ ) were not different (Table 2).

### Outcome measures

After 12 weeks, pill count adherence rate increased significantly from baseline in both study groups. In the multi-component intervention group adherence rate increased from  $92.21 \pm 14.05$  to  $97.59 \pm 10.07$  ( $P = 0.002$ ) and single intervention group adherence rate increased from  $88.60 \pm 19.66$  to  $92.42 \pm 14.27$  ( $P = 0.044$ ) (Table 3). However, the mean differences between the multi-component intervention group and the single intervention group were not significant ( $5.38 \pm 12.90$  vs  $3.18 \pm 14.23$ ,  $P = 0.531$ ) (Table 4).

**Table 1** Baseline patient characteristics

Variables	Single intervention group (N=59)	Multi-component intervention group (N=60)
Female (%)	83.1	85
Age (years, mean $\pm$ SD)	57.20 $\pm$ 12.24	55.82 $\pm$ 11.25
Education attainment (n, %)		
Under bachelor's degree	69.5	75
Bachelor's degree or above	30.5	25
Years of education (years, mean $\pm$ SD)	11.14 $\pm$ 4.32	10.98 $\pm$ 4.12
Employment status (n, %)		
Employed	64.4	56.7
Unemployed	35.6	43.3
Income (10,000 baht/month, mean $\pm$ SD)	1.25 $\pm$ 1.36	1.49 $\pm$ 1.86
Marital status (n, %)		
Single	15.3	10
Married	59.3	70
Divorce	11.9	5
Widow	13.6	15
Social health protection scheme (n, %)		
CSMBS	49.2	56.7
Non-CSMBS	50.8	43.3
Underlying disease (n, %)		
Diabetes mellitus	5.1	10
Hypertension	37.3	36.7
Dyslipidemia	32.2	31.7
Coronary artery disease	1.7	5
Chronic lung disease	1.7	3.3
Chronic kidney disease	0	1.7
Osteoporosis	27.1	18.3
History of alcohol use (n, %)	30.5	28.3
History of smoking (n, %)	15.3	10
Anxiety (n, %)	0	10
Depression (n, %)	1.7	6.7
Cognitive impairment (n, %)		
TMSE	11.9	5
MoCA-T	62.7	53.3
B-IPQ domain (mean $\pm$ SD)		
Consequences	4.03 $\pm$ 2.64	3.72 $\pm$ 2.74
Timeline	5.58 $\pm$ 3.37	5.87 $\pm$ 3.62
Personal control	5.76 $\pm$ 2.85	6.65 $\pm$ 2.90
Treatment control	8.25 $\pm$ 2.20	8.60 $\pm$ 2.25
Identity	3.97 $\pm$ 2.48	4.08 $\pm$ 2.66
Concern	4.00 $\pm$ 3.17	4.03 $\pm$ 3.32
Emotional responses	7.59 $\pm$ 2.36	7.73 $\pm$ 2.82
Illness comprehensibility	4.15 $\pm$ 3.02	3.82 $\pm$ 3.24

**Abbreviations:** B-IPQ, brief illness perception questionnaire; CSMBS, civil servants' medical benefit scheme; HADS, hospital anxiety and depression scale; MoCA-T, Thai version of Montreal cognitive assessment; TMSE, Thai mental state examination.

Sulfasalazine had the lowest adherence rate among other DMARDs. After 12 weeks, adherence rate of sulfasalazine use increased in both groups. In the multi-component intervention group, adherence rate increased from 87.39 $\pm$ 19 to 97.87 $\pm$ 15.87 ( $P=0.008$ ) and in the single intervention group, it increased from 87.94 $\pm$ 17.27 to 97.74 $\pm$ 8.27 ( $P=0.001$ ). However, the mean differences between both

groups were not significant 10.48 $\pm$ 23.05 vs 9.80 $\pm$ 16.64, ( $P=0.887$ ). Adherence rate of methotrexate use improved only in the multi-component intervention group 5.76 $\pm$ 16.78, ( $P=0.024$ ). The other drugs' adherences were not significantly changed (Table 3).

MTB score improved in the multi-component intervention group (1.12 $\pm$ 2.22,  $P<0.001$ ), but not in the single

**Table 2** Baseline disease and treatment characteristics

Variables	Single intervention group (N=59)	Multi-component intervention group (N=60)
Disease duration (years, mean $\pm$ SD)	7.73 $\pm$ 6.93	8.29 $\pm$ 7.91
Duration of treatment (years, mean $\pm$ SD)	7.14 $\pm$ 6.59	8.07 $\pm$ 7.94
Extra-articular manifestation (%)		
Sicca	57.6	68.3
Rheumatoid nodule	33.9	46.7
Interstitial lung disease	28.8	41.7
Cervical spine involvement	0.0	6.7
Cervical spine involvement	6.8	3.3
Autoantibodies		
RF positive (N=116) (n, %)	71.2	70.0
ACPA positive (N=92) (n, %)	54.2	56.7
Number of medications (mean $\pm$ SD)	7.47 $\pm$ 2.18	7.17 $\pm$ 2.34
Type and dosage of DMARDs		
MTX use (n, %)	76.3	81.7
MTX dosage (mg/week, mean $\pm$ SD)	12.17 $\pm$ 3.94	12.14 $\pm$ 4.33
SSZ use (n, %)	62.7	65.0
SSZ dosage (g/day, mean $\pm$ SD)	1.92 $\pm$ 0.76	1.94 $\pm$ 0.70
HCQ use (n, %)	27.1	28.3
HCQ dosage (mg/day, mean $\pm$ SD)	179.46 $\pm$ 44.26	179.82 $\pm$ 45.78
CQ use (n, %)	16.9	8.3
CQ dosage (mg/day, mean $\pm$ SD)	219.70 $\pm$ 65.09	200.00 $\pm$ 68.47
LEF use (n, %)	20.3	25.0
LEF dosage (mg/day, mean $\pm$ SD)	12.13 $\pm$ 6.44	14.19 $\pm$ 5.73
Prednisolone use (n, %)	32.2	40.0
Prednisolone dosage (mg/day, mean $\pm$ SD)	5.43 $\pm$ 3.11	4.18 $\pm$ 2.75
Biologics use (n, %)	1.7	1.7
History of adverse drug reaction (n, %)	20.3	33.3
DAS28 (mean $\pm$ SD)	3.24 $\pm$ 1.19	3.20 $\pm$ 0.90
EQ-5D (mean $\pm$ SD)	0.85 $\pm$ 0.12	0.82 $\pm$ 0.17
EQ-VAS (mean $\pm$ SD)	79.66 $\pm$ 15.62	77.92 $\pm$ 20.92
VAS pain (mean $\pm$ SD)	19.14 $\pm$ 20.17	18.33 $\pm$ 21.48
VAS PhGA mm, (mean $\pm$ SD)	14.66 $\pm$ 17.29	13.90 $\pm$ 17.03
Pill count adherence rate (%)	88.60 $\pm$ 19.66	92.21 $\pm$ 14.05
Good adherence <sup>a</sup> (n, %)	16.7	27.1
MTB-Thai 0–24, (mean $\pm$ SD)	21.61 $\pm$ 2.67	21.68 $\pm$ 1.91
Good adherence <sup>b</sup> (n, %)	33.3	28.8

**Notes:** <sup>a</sup>Good adherence defined as pill count adherence rate >80%. <sup>b</sup>Good adherence defined as MTB-Thai  $\geq$ 22.

**Abbreviations:** ACPA, anti-citrullinated protein antibody; CQ, chloroquine; EQ-5D, EuroQol 5 dimensions; EQ-VAS, EuroQol visual analog scale; DAS28, disease activity score 28; DMARDs, disease-modifying anti-rheumatic drugs; HCQ, hydroxychloroquine; LEF, leflunomide; MTB-Thai, Medication taking behavior questionnaire for Thai patient; MTX, methotrexate; RF, rheumatoid factor; SSZ, sulfasalazine; VAS pain, visual analog scale for pain; VAS PhGA, visual analog scale for physician global assessment.

intervention group (0.44 $\pm$ 2.92,  $P=0.0251$ ). DAS28, EQ-5D, EQ-VAS, pain, and PhGA were unchanged from baseline in both groups. There was no difference in the proportion of patients who had anxiety or depression. Illness perceptions remained unchanged (Tables 3 and 4).

## Discussion

During a 12-week period, adherence rate measured by pill count in both groups (single intervention and multi-component intervention) were significantly improved. However, MTB score improved only in multi-component

intervention group. Both pill count and MTB score are indirect measurements of adherence.<sup>31</sup> The result of pill count method is more reliable than MTB score because MTB score is a questionnaire that patients report by themselves. The data suggested that patient education could improve medication adherence. However, there were no differences between single intervention and multi-component intervention groups in improving medication adherence.

A number of intervention trials have been conducted to enhance adherence to treatment in patients with immune-mediated inflammatory disorders, including information



**Table 3** Disease parameters at baseline and 12 weeks of the single and multi-component intervention groups

Variables	Single intervention group (N=59)			Multi-component intervention group (N=60)		
	At baseline	At 12 weeks	P-value	At baseline	At 12 weeks	P-value
Pill count adherence rate (%)	88.60±19.66	92.42±14.27	0.044	92.21±14.05	97.59±10.07	0.002
Good adherence <sup>a</sup> (n, %)	72.9	89.8	0.019	83.3	95	0.040
Adherence rate per each medication						
MTX (%)	89.76±19.96	92.60±15.01	0.190	92.61±16.05	98.37±9.70	0.024
SSZ (%)	87.94±17.27	97.74±8.27	0.001	87.39±19.00	97.87±15.87	0.008
HCO (%)	88.06±35.80	87.07±16.00	0.893	89.38±24.20	90.32±24.87	0.628
CQ (%)	95.32±11.80	96.19±13.50	0.788	105.18±4.40	103.94±7.53	0.585
LEF (%)	87.95±16.04	98.57±15.00	0.143	100.84±15.78	97.18±9.31	0.438
Prednisolone (%)	94.12±13.69	94.26±11.91	0.975	90.95±20.52	97.45±7.00	0.181
MTB score (mean ± SD)	21.61±2.67	22.05±1.91	0.251	21.68±1.91	22.80±1.34	<0.001
Good adherence <sup>b</sup> (n, %)	71.2	71.2	1.000	66.7	85	0.020
DAS28 (mean ± SD)	3.24±1.19	3.17±1.23	0.563	3.20±0.90	3.01±1.05	0.160
EQ-5D (mean ± SD)	0.850±0.123	0.825±0.136	0.142	0.823±0.175	0.824±0.177	0.945
EQ-VAS (mean ± SD)	79.66±15.62	74.64±20.51	0.055	77.92±20.92	76.08±21.35	0.577
VAS pain (mean ± SD)	19.41±20.17	20.00±23.27	0.840	18.33±21.48	12.58±17.72	0.092
VAS PhGA (mean ± SD)	14.66±17.29	17.29±20.75	0.272	13.90±17.03	10.12±15.62	0.159
Anxiety <sup>c</sup> (n, %)	0	1.7	0.317	10	3.3	0.142
Depression <sup>c</sup> (n, %)	1.7	3.4	0.560	6.7	3.3	0.724
B-IPQ domain (mean ± SD)						
Consequences	4.03±2.64	3.47±2.57	0.160	3.73±2.77	3.54±2.98	0.594
Timeline	5.58±3.37	5.47±3.37	0.842	5.92±3.63	6.32±3.47	0.423
Personal control	5.76±2.85	6.07±2.77	0.501	6.66±2.93	6.19±3.12	0.268
Treatment control	8.25±2.02	7.83±2.08	0.173	8.64±2.24	8.54±2.03	0.778
Identity	3.94±2.48	3.80±2.34	0.621	4.12±2.67	3.95±2.63	0.621
Concern	4.00±3.17	4.19±2.84	0.587	4.07±3.34	4.08±3.13	0.972
Emotional responses	7.59±2.36	7.78±1.90	0.551	7.75±3.84	7.95±2.47	0.670
Illness comprehensibility	4.15±3.02	4.44±3.05	0.520	3.81±3.27	3.49±2.94	0.329

**Notes:** <sup>a</sup>Good adherence defined as pill count adherence rate >80%. <sup>b</sup>Good adherence defined as MTB-Thai ≥22. <sup>c</sup>Anxiety and depression defined as HADS score >10.

**Abbreviations:** B-IPQ, brief illness perception questionnaire; CQ, chloroquine; DAS28, disease activity score 28; EQ-5D, EuroQol 5 dimensions; EQ-VAS, EuroQol visual analog scale; HADS, hospital anxiety and depression scale; HCO, hydroxychloroquine; LEF, leflunomide; MTB-Thai, medication taking behavior questionnaire for Thai patient; MTX, methotrexate; SSZ, sulfasalazine; VAS pain, visual analog scale for pain; VAS PhGA, visual analog scale for physician global assessment.

about disease,<sup>41</sup> medication reminders using pillbox or mobile phone,<sup>56</sup> and motivational interview.<sup>57</sup> A recent systemic analysis revealed that multi-component interventions showed the greatest evidence for promoting adherence in patients.<sup>36</sup> However, this systematic analysis found a high level of heterogeneity in study methods as well as little consistency in their conclusions,<sup>9,40,58,59</sup> which does not allow us to draw clear assumptions about the interventions intended to improve medication adherence.

A British randomized controlled study of RA patients revealed that patient education was correlated with adherence.<sup>41</sup> One hundred active RA patients were randomized to an intervention group, which received seven 30-minute one-on-one sessions with a rheumatology nurse directed at improving self-efficacy, or a control group, which received standard treatment (providing a drug information pamphlet). After 6 months, those in the intervention group were more

adherent to drugs. In contrast, a less intensive intervention involving two pharmacist-led motivational interviewing group sessions failed to improve DMARDs adherence more than providing information regarding their medications.<sup>60</sup>

Our study showed no differences between single intervention and multi-component interventions in improving medication adherence. This implied that educational interventions, which deliver instructive information alone, may lead to improved medication adherence. However, the 30-minute directed counseling with provision of brochures did not provide any add-on benefit. One explanation for the imperfect effect of these educational interventions may be that provision of information presumes the patient lacks understanding of their disease and medications. This attributes a passive role to the patient and fails to reflect pre-existing "lay beliefs" acquired from other sources, for example, the newspapers, social media, or friends and family.<sup>18</sup> A successful educa-

**Table 4** Mean changes in disease parameters from baseline until the 12-week follow-up in both single and multi-component intervention groups

Variables	Single intervention group (N=59)	Multi-component intervention group (N=60)	P-value
	Mean difference	Mean difference	
Pill count adherence rate (%)	3.81±14.23	5.38±12.90	0.531
Adherence rate per each medication			
MTX (%)	2.83±13.45	5.76±16.78	0.379
SSZ (%)	9.80±16.64	10.48±23.05	0.887
HCQ (%)	-0.99±28.73	0.94±7.84	0.792
CQ (%)	0.87±9.88	-1.24±4.68	0.662
LEF (%)	10.62±18.20	-3.66±15.74	0.078
Prednisolone (%)	0.14±17.59	6.50±21.47	0.342
MTB score (mean ± SD)	0.44±2.92	1.12±2.22	0.157
DAS28 (mean ± SD)	-0.07±0.89	-0.20±1.06	0.476
EQ-5D (mean ± SD)	-0.025±0.131	0.002±0.173	0.341
EQ-VAS (mean ± SD)	-5.02±19.71	-1.83±25.31	0.446
VAS pain (mean ± SD)	0.59±22.52	-5.75±25.99	0.158
VAS PhGA (mean ± SD)	2.63±18.20	-3.78±20.56	0.074
B-IPQ domain (mean ± SD)			
Consequences	-0.56±3.02	-0.19±2.67	0.479
Timeline	-0.10±3.90	0.41±3.87	0.478
Personal control	0.31±3.46	-0.47±3.26	0.210
Treatment control	-0.42±2.36	-0.10±2.76	0.479
Identity	-0.17±2.62	-0.17±2.62	1.000
Concern	0.19±2.62	0.02±3.68	0.774
Emotional responses	0.19±2.39	0.20±3.65	0.976
Illness comprehensibility	0.29±3.42	-0.32±2.52	0.272

**Abbreviations:** B-IPQ, brief illness perception questionnaire; CQ, chloroquine; DAS28, disease activity score 28; EQ-5D, EuroQol 5 dimensions; EQ-VAS, EuroQol visual analog scale; HCQ, hydroxychloroquine; LEF, leflunomide; MTB-Thai, medication taking behavior questionnaire for Thai patient; MTX, methotrexate; SSZ, sulfasalazine; VAS pain, visual analog scale for pain; VAS PhGA, visual analog scale for physician global assessment.

tional intervention may require participation from both the physician and patient. Admittedly, some patients may wish to entrust most of the decision making to their treating physician. It is, therefore, crucial to determine how involved the patient wishes to be in constructing the management plan.<sup>61</sup> As soon as this is established, a proper educational intervention could involve intertwining biomedical information into pre-existing lay belief systems.<sup>18</sup>

Although education interventions in this study improved adherence to DMARD treatment, as in other studies, this boosted adherence did not produce considerable additional beneficial clinical outcome.<sup>37,62,63</sup> Possibly, the composite index for measuring disease activity and quality of life might not have been a sensitive indicator to detect trivial changes between the two groups.

## Limitations

This study had several limitations. First, patient's adherence is challenging to measure and all techniques have

downsides. Both self-reported questionnaire and pill count methods tend to overestimate adherence behavior and generally have low sensitivity.<sup>64,65</sup> Second, a 12-week study period may perhaps be too short to affect the clinical outcome. A longer time period might be needed to demonstrate maximal efficacy. Third, nearly one-fourth of patients in this trial reported a perception of having experienced adverse drug reactions. This perception of medication side effects may affect their adherence. Finally, this study did not assess patients' health literacy. Patients require sufficient literacy to comprehend medication instructions and calculate accurate medication doses to be taken for the suitable duration.<sup>66,67</sup> Poor health literacy is linked to a range of unfavorable health outcomes possibly due to improper self-care, incomplete health responsibility, and under-utilization of available healthcare resources. Methods to augment health literacy, rather than providing disease information might be valuable in enhancing medication adherence.



## Conclusion

Patient education significantly improves adherence. However, in this study, there were no differences between single education intervention and multi-component education intervention in improving medication adherence. Provision of disease information pamphlet with or without directed counseling can equally improve medication adherence of patients with RA.

## Data sharing statement

Individual participant data that underlie the results reported in this article, after deidentification, information pamphlet, and study protocol, are available on request from the corresponding author after article publication.

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## Disclosure

The authors report no conflicts of interest in this work.

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