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Original Article

What are the risk factors of poor medication adherence in the target-to-treat era?

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ABSTRACT

Objectives: This study aims to identify adherence rate and risk factors of poor adherence in patients with tightly controlled rheumatoid arthritis (RA) based on the treat-to-target (TTT) strategy.

Patients and methods: In this cross-sectional, observational study, a total of 103 patients (22 males, 81 females; mean age 58.6±9.5 years; range, 35 to 76 years) with tightly controlled RA between November 2016 and May 2017 were included. The patients were evaluated in terms of sociodemographic features, smoking and alcohol drinking status, body mass index (BMI), Disease Activity Score 28 (DAS28), and clinical and medication data. They filled out a series of standardized questionnaires including the Morisky 8-item Medication Adherence Scale (MMAS-8), Beck Depression Inventory (BDI), Mini-Mental State Examination (MMSE), and Health Assessment Questionnaire-Disability Index (HAQ-DI). Multiple multivariate linear regression analysis was used to identify variables which were possibly associated with the MMAS-8.

Results: Of the patients, 53 (51.5%) were non-adherent and 50 (48.5%) were adherent to medication. The DAS28-erythrocyte sedimentation rate, mean DAS28, HAQ, BDI scores, and the number of visits were higher and the MMSE scores were lower in non-adherent patients than adherent patients. In the linear multivariate analysis, significant associations were found between the MMAS-8 and MMSE, BDI, DAS28, and mean DAS28 scores.

Conclusion: Our study results show that the medication adherence rate is significantly higher compared to previous studies and high disease activity, depression, and cognitive dysfunction significantly affect medication adherence in this patient population.

Keywords: Cognitive dysfunction; depression; medication adherence; rheumatoid arthritis.

Rheumatoid arthritis (RA) is a chronic progressive inflammatory illness which affects almost 1% of the population and requires continuous treatment with various drugs.[1] Although extremely effective medications have been developed for RA in recent years, an adequate response to treatment cannot be reached in some patients due to several reasons, such as different response to medication or poor adherence to therapy.[2] Medication adherence can be defined as the behavior about taking drugs that fits with the physician's advice.[3] Poor medication adherence in the RA population may cause unnecessary changes in the treatment, increased morbidity and mortality, and waste of health care resources. Therefore, it is essential to investigate medication adherence and the possible factors affecting medication adherence in patients with RA.[4] Patients' characteristics, disease characteristics, and medication factors have been demonstrated to influence medication adherence in this population.[5,6] In addition, it has been shown that poor communication between health care providers and patients, failing to highlight the effectiveness and side effects of drugs, leads to poor medication adherence.[7] It has been demonstrated that regular visits with rheumatologists, stable patient-physician connection, and adequate information about RA treatment provide better adherence.[5,7,8]

Recently, individually-tailored management strategies including early, aggressive treatment, and close follow-up of response to treatment aiming at

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low disease activity, ideally remission, have become the main strategy of treatment in RA. This strategy, treat-to-target (TTT), has been demonstrated to be more successful than earlier management practices in managing inflammation and avoiding the augmentation of joint damage.[9,10] Most of the previous studies assessing barriers to patient medication adherence in RA were not conducted in the context of the TTT approach and the earlier stated risk factors of nonadherence may not apply in these patients.[3] Therefore, in the present study, we aimed to investigate the adherence rate and risk factors of poor adherence in patients with tightly controlled RA based on the TTT strategy.

PATIENTS AND METHODS

This cross-sectional, observational study was conducted in our outpatient clinic of the Physical Medicine and Rehabilitation Department and included a total of 103 patients (22 males, 81 females; mean age 58.6±9.5 years; range, 35 to 76 years) with tightly controlled RA between November 2016 and May 2017. *Inclusion criteria were as follows:* having a diagnosis of RA according to the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) 2010 criteria,[11] aged least 18 years old, and under follow-up regularly in our clinic for at least three years. A written informed consent was obtained from each patient. The study protocol was approved by the Ankara Numune Training and Research Hospital Ethics Committee (E-16-1090). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Our team which has adopted TTT approach consists of specialist physicians and the other health professionals. We meet regularly for RA patients to evaluate the disease activity, drug side effects, and when necessary, to modify the drug regimen for achieving remission or minimal disease activity. All patients are informed about their disease, treatment options, and possible side effects on a regular basis. The periodicity of visits is every 12 weeks, after each visit, the next date for each patient is planned and recorded. Patients are evaluated in between the scheduled visits, if necessary, due to reasons such as side effects and increased disease activity.

Participants were excluded, if they did not come to the visits regularly, had mental disorders, and had shorter follow-up interval than three years. Socio-demographic data, smoking and alcohol drinking status, the number of visits within one year before the evaluation date, body mass index (BMI), and clinical and medication data were recorded. The Disease Activity Score 28-eryhtrocyte sedimentation rate (DAS28-ESR) at the evaluation date and the mean DAS28 during one-year follow-up before the evaluation date were recorded using follow-up visit charts. All included patients filled out a series of standardized questionnaires including the Morisky 8-item Medication Adherence Scale (MMAS-8), Mini-Mental State Examination (MMSE), Beck Depression Inventory (BDI), and Health Assessment Questionnaire-Disability Index (HAQ-DI).

The BMI was measured utilizing the formula: BMI (kg/m^2)= Weight (kg)/(Height)^2(m^2). Body mass index grades were classified as low (<20 kg/m^2), normal (20-25 kg/m^2), overweight (25-30 kg/m^2), and obese (>30 kg/m^2).[12]

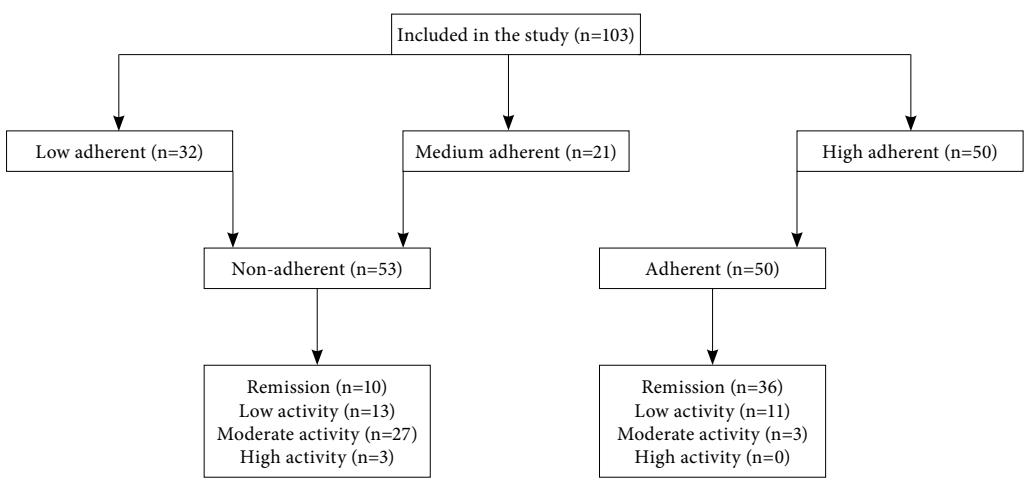

Figure 1. Study flow chart.

Medication adherence was measured using the validated Turkish version of the MMAS-8.[13] It is a common survey consisting of eight questions to evaluate self-reported medication-taking behavior. According to the MMAS-8 scoring system, lower than 6 points are graded as low, 6-7 points as medium, and 8 points as high adherence. The patient's low or medium adherent is defined as non-adherent.[7,14]

The BDI was employed to test the depressive symptoms. The BDI is a 21-item, each scored from 0-3, self-rated scale which evaluates key symptoms of the depression. The cut-off marks show minimal or no depression (until 13), mild depression (14-19), moderate depression (20-28), and severe depression (29-63).[15-17]

The MMSE was used to evaluate cognitive functions. The MMSE is a 30-item cognitive assessment which evaluates orientation, attention, memory, and language. Any scores higher than or equal to 27 points are considered as normal. Other scores are graded as severe (<10), moderate (11-20) and mild (21-26) cognitive failure.[18-20]

Functional impairment was measured using the HAQ-DI which consists of 20 components in eight domains (i.e., dressing and grooming, arising, eating, walking, hygiene, grip, reach, and other common activities). The answer options are no difficulty (0), with some difficulty (1), with much difficulty (2), unable to do (3). HAQ-DI score is between 0-3, with greater scores pointing higher disability.[21,22]

Evaluation of RA activity was made using the DAS28-ESR. It is calculated by adding the number of swollen joints, tender joints, ESR value, and patient self-reported visual analog scale (VAS) pain score. The scores indicate remission (<2,6), low disease activity (≤3.2), moderate disease activity (3.3-5.1), and high disease activity (>5.1).[23]

Statistical analysis

Statistical analysis was performed using the PASW for Windows version 18.0 software (SPSS Inc., Chicago, IL, USA). The effect size (Cohen's d value) was found to 1.3 for DAS28 score's mean differences of the two main groups (effect size varied between 0.6-1.3 for different variables). Post-hoc power analyses were performed with using G*Power 3.0.10 program (Heinrich-Heine-Universität, Düsseldorf, Düsseldorf, Germany) and power of the study (1-β) was calculated as 0.85 (alpha coefficient is accepted as 0.05, effect size was accepted 0.6 and tails were accepted two).[24,25] The Cronbach's alpha was 0.74 for internal consistency of Morisky

Table 1. Baseline demographic characteristics of patients

	Adherent (n=50)					Non-adherent (n=53)					Total (n=103)				
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			58.98±9.48					58.22±10.55					58.61±9.48			0.51*
Gender																0.744**
Female	40	80				41	77.4				81	78.6				
Marital status married	36	72				42	79.2				78	75.7				0.391**
Current smokers	1	2				5	9.4				6	5.8				0.107†
Educational level illiterate	10	20				17	32.1				27	26.2				0.164-**
Occupation non-employed	36	72				40	75.5				76	73.8				0.648**
Household monthly income (₺)			1,543.39±646.44	1,300	500-3,500			1,587±1,419.71	1,300	300-10,000			1,564.56±1,087.10	1,300	300-10,000	0.196‡
Regular alcohol consumption	1	2				2	3.8				3	2.9				0.593¥
Body mass index (kg/m^2)																
Underweight	0	0				1	1.9				1	1				
Normal weight	17	34				14	26.4				31	30.1				
Overweight	18	36				16	30.2				34	33				
Obesity	15	30				22	41.5				37	36				

SD: Standard deviation; Min: Minimum; Max: Maximum; ₺: Turkish lira sign; * Chi-square test; ** T test; † Fisher Exact test; ‡ Mann-Whitney U test; P<0.05 was accepted statistically significant.

scale which is consisted of eight items. Cronbach's alpha >0.70 was acceptable.[26]

The Shapiro-Wilk test was used to test normality. According to test results, parametric and non-parametric tests were applied. Overall descriptive statistics were expressed in mean ± standard deviation (SD) and median (min-max) values for continuous variables. Categorical data were expressed in number and percentage. The independent sample t-test (for parametric variables), Mann-Whitney U (for non-parametric variables), chi-square (for nominal variables), and Fisher exact test (for nominal variables lower than five in each group) were used to compare the groups. Significant predictors for medication adherence were evaluated. The Spearman's correlation coefficient was utilized to analyze the association among the MMAS-8 score and age, disease duration, number of drugs, number of visits, BDI, MMSE, HAQ, and DAS28 values. Multiple multivariate linear regression analysis was, then, performed to identify variables that were possibly associated with the MMAS-8 scores. Regression analyses met the assumptions including linear relationship between the medication adherence score and the independent variables; homoscedasticity; independence of observations; appropriate sample size. R^2 value, that was found 0.32, shows the generalizability of the model. If the model was produced in the universe rather than in the sample, it would account for 32% of the total variance. A p value of <0.05 was considered statistically significant.

RESULTS

Of the patients, 53 (51.5%) were non-adherent and 50 (48.5%) were adherent to medication. Among these patients, 32 (31.1%) showed low adherence, 21 (20.4%) showed medium adherence, and 50 (48.5%) showed high adherence to medication. The study flow chart is shown in Figure 1.

According to the medication adherence, patients' socio-demographic features, smoking and alcohol consumption status, BMI, comorbidities, and medications are shown in Table 1 and Table 2. The age, gender, marital status, education level, comorbidities, occupation, BMI score, smoking and alcohol intake, household monthly income, and route of administration

Table 2. Comorbidities and treatments of rheumatoid arthritis patients

	Adherent (n=50)		Non-adherent (n=53)		Total (n=103)		
Variables	n	%	n	%	n	%	*p*
Comorbidity							
Without comorbidity	18	36	13	24.5	31	30.1	
Hypertension	19	38	25	47.2	44	42.7	
Diabetes mellitus	5	10	9	17	14	13.5	
Chronic pulmonary disease	6	12	10	18.9	16	15.5	0.205*
Cerebrovascular disease	1	2	2	3.8	3	2.9	
Ischemic heart disease	2	4	7	13.2	9	8.9	
Thyroid disease	3	6	4	7.5	7	6.8	
Drug therapy							
Parenteral route of administration	10	20	4	7.5	14	13.5	
Methotrexate	22	44	32	60.4	54	52.4	
Hydroxychloroquine	20	40	20	37.7	40	38.9	
Prednisolone	22	44	32	60.4	54	52.4	
Biologics	5	10	2	3.8	7	6.8	0.059*
Methotrexate sc	5	10	2	3.8	7	6.8	
Leflunomide	8	16	11	20.7	19	18.5	
Sulfasalazine	8	16	6	11.4	14	13.5	
Tofacitinib	1	2	1	1.9	2	1.9	

* Chi-square test; P<0.05 was accepted statistically significant.

Table 3. Clinical characteristics of patients

	Adherent MMAS-8=8 (n=50)					Non-adherent MMAS-8<8 (n=53)					Total (n=103)				
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Numbers of medication taken except rheumatoid arthritis			2.48±1.59	2	0-6			3.01±2.16	3	0-11			2.57±1.91	2	0-11	0.207†
Duration of disease (year)			16.41±8.59	16	2-32			16.09±8.76	16	2-40			16.24±8.64	16	2-40	0.776†
Number of visits within one year follow-up before the evaluation date			4.96±1.42	4	3-9			6.24±1.95	6	4-14			5.62±1.82	5	3-14	<0.001†
HAQ			0.41±0.43	0.27	0-1.50			0.86±0.55	0.80	0.05-2.70			0.64±0.54	0.50	0-2.70	<0.001†
BDI			5.24±6.92	3	0-29			10.52±9.81	6	0-42			7.96±8.89	5	0-42	0.003†
MMSE			28.52±1.77	29	24-30			27±2.94	28	19-30			27.73±2.55	29	19-30	0.009†
DAS28-ESR			2.30±0.71					3.34±0.99					2.83±1.00			<0.001*
DAS28-ESR mean‡			2.46±0.78					3.40±0.98					2.94±1.00			<0.001*
Disease activity																<0.001**
Remission	36	72				10	18.9				46	44.7				
Low	11	22				13	24.5				24	23.3				
Moderate	3	6				27	50.9				30	29.1				
High	0	0				3	5.7				3	2.9				

SD: Standard deviation; Min: Minimum; Max: Maximum; HAQ: Health Assessment Questionnaire; BDI: Beck Depression Inventory; MMSE: Mini-Mental State Examination; DAS28: Disease Activity Score 28; ESR: Erythrocyte sedimentation rate; * T test; ** Chi-square test; † Mann-Whitney U test; P<0.05 was considered statistically significant; ‡ DAS28 mean rate in the past one year.

of the drug did not differ between the non-adherent and adherent patients.

The comparisons among the non-adherent and adherent patients in terms of the number of drugs used except RA, disease duration, disease activity, the number of visits, HAQ-DI, BDI, and MMSE scores are summarized in Table 3. The DAS28-ESR, mean DAS28-ESR, HAQ-DI, BDI scores, and the number of visits were higher, while the MMSE scores were lower in the non-adherent patients than adherent patients (p<0.001).

We found a significant correlation between the MMAS-8 and DAS28, mean DAS28, HAQ-DI, BDI, number of visits (all p<0.001) and MMSE (p=0.003). Multiple linear regression was used to evaluate the influence of the clinical variables on medication adherence. The MMSE, BDI, DAS28, and mean DAS28 scores were found to be associated with medication adherence. Higher scores on the Morisky scale indicates more problems with medication adherence and the regression coefficient indicated that relationship among clinical variables and poor adherence is the strongest for the change in DAS28 value (β=-0.51) (Our sample size was in accordance with the independent variable number: N >50+8 m (m=number of independent variables).[27] In this study, we had five independent variables, thus requiring a sample size of at least 90 participants. This assumption has been met due to having a sample including 103 patients. Our plot of standardized residuals showed no obvious signs of funneling; suggesting the assumption of homoscedasticity has been met. The Durbin-Watson statistic showed that the values of the residuals were independent, and the Durbin-Watson (=1.93) value was close to 2 (Table 4).

DISCUSSION

In the current study, we aimed to explore medication adherence rate and the risk factors of poor adherence in the TTT context. Our findings suggested that our adherence rate was significantly higher than previous studies using MMAS-8, and disease activity and functionality were better in adherent patients, and lower adherence was related to high disease activity, high mean disease activity, the patients' depressive symptoms, and low cognitive level.

Several studies showed that the medication adherence rates to prescribed medicine protocols in the RA population might change at 30 to 80%, depending on the use of different methods.[4]

Table 4. Relationship between Morisky 8-item Medication Adherence Scale and clinical variables

Morisky 8-item Medication Adherence Scale	B	SE	*p**	95% CI	
Mini-Mental State Examination	0.09	0.03	0.003	0.03	0.16
Beck Depression Inventory	-0.03	0.01	0.001	-0.05	-0.01
Disease Activity Score 28	-0.51	0.07	<0.001	-0.65	-0.37
Disease Activity Score 28 mean†	-0.38	0.08	<0.001	-0.55	-0.22
Health Assessment Questionnaire	-0.30	0.16	0.06	-0.61	0.01
(R^2=0.32, F=23.31)					

B: Regression coefficient; SE: Standard error; Cl: Confidence interval; * Multivariate regression analyses; R^2: Coefficient of determination; † Disease Activity Score 28 mean rate in the past one year.

There is no particularly recommended approach to measure medication adherence, and each approach has positive and negative sides. However, employing a validated, and reliable standardized query offers certain benefits.[7] It provides both relatively reliable measurement and comparison with previous studies using the same questionnaire. The present study evaluated the adherence rate using the MMAS-8 which was commonly used in previous reports. Unlike other studies, our study focused on medication adherence to only RA patients who were informed and followed regularly based on the TTT strategy in the outpatient setting. This strategy has become the standard of care for RA, due to the improved outcomes in clinical practice.[9] However, to the best of our knowledge, there are no studies investigating medication adherence in RA patients under follow-up regularly in the TTT context.[3] Our adherence rate demonstrated that 51.5% of the participants had low or medium adherence and 48.5% had high adherence to RA medication. This study showed a higher prevalence of medication adherence in patients with RA in contrast to previous studies using MMAS-8 (Figure 2).[7,28-30] In addition, several reports have demonstrated the importance of regular visits to the physician, adequate patient contact time in clinical practice, and patient education to improve medication adherence to treatment; however, it has not been well-studied for RA patients.[31] Although there is no study to measure medication adherence using MMAS-8 in patients with RA in Turkey, the higher medication adherence rates than previous studies using MMAS-8 in other countries may emphasize the importance of tight control and the strong patient-physician interaction on medication adherence.

Another goal of the current study was to assess risk factors for poor medication adherence. Although significant correlations were found between the MMAS-8 and DAS28, the mean DAS28, HAQ-DI, MMSE, BDI, and number of visits, in the multiple linear regression analyses, only DAS28, mean DAS28,

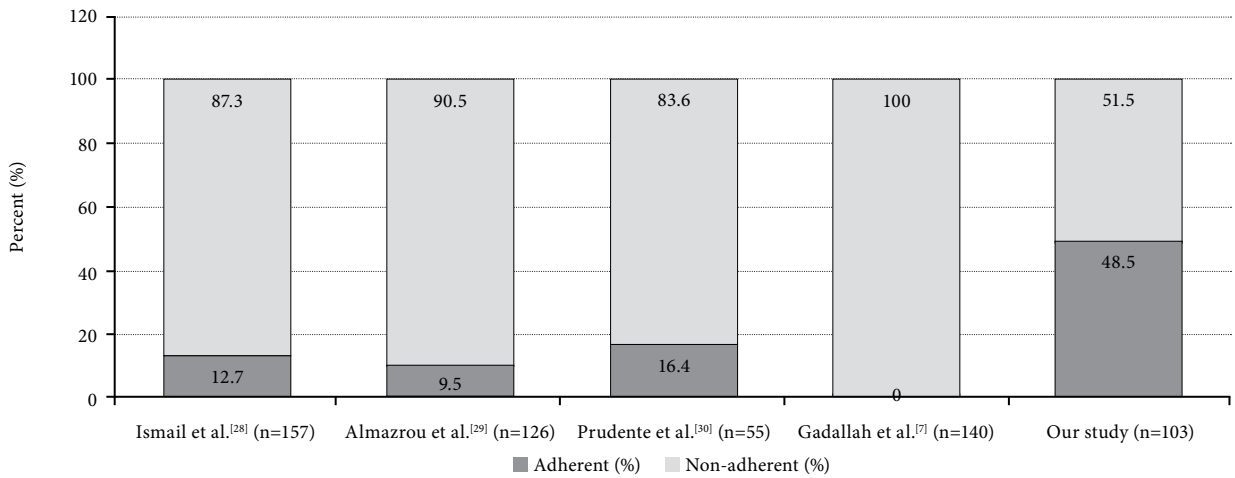

Figure 2. The medication adherence rates in the studies using Morisky 8-item Medication Adherence Scale.

MMSE, and BDI were found to be significant. The literature already revealed that poor adherence to medication in the patients with RA was related to high disease activity and more disability.[32] That is true, however, high disease activity may only not a result, but may also be a reason for the poor medication adherence. According to our multivariate analysis, the relationship between poor medication adherence and high disease activity supports this hypothesis. High disease activity may reduce the patients' reliance on therapeutic approach, which may lead to medication non-adherence, which may further increase the disease activity. In clinical practice, the necessary precautions must be taken to break this vicious circle.

According to multivariate analysis, the risk factors of poor adherence except disease activity were the patients' depressive symptoms and low cognitive level. The relationship between poor medication adherence and depression in RA patients has been previously shown in several studies.[33,34] There are some causes why depression may be related to medication non-adherence. Not believing the benefit of treatment due to feelings of hopelessness, lacking of the energy, and focus necessary to follow through with treatment advice, and being more vulnerable to side effects are the important causes of non-adherence to treatment in depressed patients.[35] In the light of this information, physicians should evaluate the medication adherence in the patients with depression and should evaluate the depression in the non-adherent patients. Treating depression in RA patients can also improve disease activity and functionality.

Finally, cognitive dysfunction increased adherence problems in this study. Similarly to our findings, Park et al.[36] demonstrated that the patients with low cognitive function had more medication adherence problems, compared to age-matched controls. Bruera et al.[37] also reported that medication reminders could support patients with RA in taking medications, particularly in patients who simply forget to take their medication. The use of medication reminders to improve medication adherence in patients with RA may be considered as an option.

Review of the literature reveals various factors as the determinants of adherence. Age, gender, disease duration, income status, occupation, multiple concomitant drugs, and the route of administration of the drug have been all shown to affect the medication adherence.[5,7,38-40] However, none of these factors was found to be associated with medication adherence in our study population.

Nonetheless, there are some limitations to this study. First, adherence to the medication was measured in a small sample size at a single center and limited with patients who were only under regular follow-up. Therefore, the generalizability of the results is limited. Second, adherence was measured a self-reported questionnaire which may produce incorrect observations and recall bias. Lastly, the cross-sectional design of this study limited our ability to evaluate causality. Therefore, further large-scale, multi-center, longitudinal studies including a control group are needed.

In conclusion, in the present study, medication adherence in RA patients who were closely followed based on the TTT strategy was significantly higher, compared to previous studies using the MMAS-8. High disease activity, depression, and cognitive dysfunction were also the main barriers to medication adherence. We achieved remission or low disease activity, which is our aim as a part of the EULAR recommendations, at rates exceeding 90% in good adherent patients. Based on these findings, in daily practice, targeted treatment is substantial, and the physician should build toward a stable and trustworthy connection with the patient by close follow-up and monitoring to reach the most optimal clinical outcomes. Nevertheless, if we do not take precautions for depression and low cognitive level, even for patients followed closely according to the TTT strategy, our management may be insufficient.

Declaration of conflicting interests

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