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Characteristics and Treatment Responses of Rheumatoid Arthritis Patients at Dr. Cipto Mangunkusumo National General Hospital

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A B S T R A C T

Introduction. Rheumatoid arthritis (RA) is a chronic progressive autoimmune rheumatic disease that primarily affects the joints. The goal of RA treatment is to achieve remission or low disease activity, using a treat-to-target approach. This study aims to explore the characteristics of RA patients and evaluate their treatment responses in Dr. Cipto Mangunkusumo National General Hospital (RSCM). **Methods.** This cross-sectional study is conducted by collecting demographic and clinical data, as well as interviewing adult patients that have been diagnosed with RA at the Rheumatology Clinic of RSCM and have been on disease-modifying antirheumatic drugs (DMARD) treatment for a minimum of 6 months. **Results.** A total of 94 patients were included in this study. Subjects were predominantly female (93.6%) and had no formal jobs (64.9%). A majority of RA patients exhibited moderate disease activity (48.9%, based on Disease Activity Score-28 with erythrocyte sedimentation rate [DAS-28 ESR]), with a relatively high level of steroid use (86.2%). Notably, most patients started DMARD treatment more than 2 years after the onset of symptoms (45.7%). The proportion of patients achieving therapy target (remission to low disease activity) was 41.5%, with 13.8% attaining remission. Furthermore, Health Assessment Quality (HAQ) scores were found to be significantly lower among the target-achieving group, indicating better quality of life. **Conclusion.** Therapy target was achieved in 41.5% of RA patients in RSCM, with 13.8% achieving remission. Further research can be conducted to evaluate factors which may affect treatment response among RA patients.

1. Introduction

Rheumatoid arthritis (RA) is a chronic and progressive autoimmune systemic disease which is primarily characterized by inflammation of the joints.[1–3] An important feature of this disease is the presence of autoantibodies against immunoglobulin G (IgG), known as the rheumatoid factor (RF), and citrullinated protein, known as anti-citrullinated protein antibodies (ACPAs).[1,3] Managing RA requires a comprehensive and continuous approach. Like many other autoimmune diseases, RA is not curable, thus the goal of treatment is to control disease activity and reach a state of remission or at least low disease activity.2 To achieve this goal, a "treat-to-target" strategy is necessary.[4] This strategy involves regularly evaluating treatment progress, aiming for disease improvement within three months and achieving remission (or at least low disease activity) within six months of therapy initiation.[4]

Recent studies indicated that only about 35.5% of RA patients in the Asia-Pacific region achieve remission (based on DAS-28 ESR). In Indonesia, this proportion is even lower, with only about 18.8%

achieving remission.[5] However, to date, there is no data available regarding the achievement of RA therapy target at Dr. Cipto Mangunkusumo National General Hospital (RSCM). Therefore, this research aims to evaluate treatment response for RA, particularly at RSCM. Additionally, the data collected on therapy target achievement is also expected help evaluate the quality of care provided to these patients.

2. Methods

This cross-sectional study was conducted at Dr. Cipto Mangunkusumo National General Hospital (RSCM). The inclusion criteria were as follows: (1) patients aged ≥ 18 years who had been diagnosed with RA based on the American College of Rheumatology (ACR) 1987 criteria or meet the ACR/EULAR (European Alliance of Associations for Rheumatology) 2010 classification criteria, (2) had received at least one disease-modifying antirheumatic drug (DMARD) therapy (conventional and/or biological) for a minimum of 6 months, and (3) had consented to participate in the study and signed the informed consent form. Patients with other autoimmune diseases (such as systemic lupus erythematosus, etc.) were excluded. This study has been approved by the Ethical Committee Board Faculty of Medicine Universitas Indonesia (KET-183/UN2.F1/ETIK/PPM.00.02/2020) and was conducted according to the ethical principles of the Declaration of Helsinki.

Eligible subjects were interviewed and underwent physical examination at the Rheumatology Clinic of RSCM. Demographic data including age, gender, education level, body weight, height, body mass index, employment status, family disease history, smoking history, and comorbidities were collected. Clinical data, including extraarticular manifestations, duration from symptoms onset to DMARD initiation, treatment duration, and treatment history (conventional DMARDs [cDMARDs], targeted synthetic DMARDs [tsDMARDs], biologic DMARDs [bDMARDs], and corticosteroid use), were also recorded. Trained physicians conducted evaluations of tender and swollen joint counts, along with physicians' global visual analogue scale (VAS) assessment, which was rated on a scale of 0 to 10 cm. Patients' pain VAS, fatigue VAS, and global VAS were also recorded on a scale of 0 to 10 cm. Laboratory data, including levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF), were collected. Health-related quality of life was assessed using the Health Assessment Questionnaire (HAQ).

RA disease activity was evaluated using both the Disease Activity Score-28 with ESR (DAS28-ESR) and DAS28 with CRP (DAS28-CRP). Patients were classified into the following categories based on their DAS28 scores: remission (≤2.6), low (>2.6 to ≤3.2), moderate (>3.2 to ≤5), and severe disease activity (>5). In this study, treatment target was considered achieved in patients with remission or low disease activity, whereas those with moderate to severe disease activity were classified into the non-achieving group.

The target-achieving and non-achieving group were compared in terms of demographic, clinical, and laboratory parameters. Categorical variables were compared using the chi-square test or Fisher's exact test as an alternative, while continuous outcomes were compared using the Mann-Whitney test. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed with Statistical Package for Social Sciences 27 (SPSS 27, IBM Corporation).

3. Results

A total of 94 patients were included in this study. Subjects were predominantly female (93.6%) and most were not formally employed (majority being housewives). Nearly all subjects had formal education, at least completing high school or its equivalent. Further details on the baseline characteristics of the subjects are presented in Table 1.

The majority of patients received methotrexate (MTX) (89.4%), followed by sulfasalazine (23.4%) as DMARD therapy, either as monotherapy or in combination. However, none of the patients received

biological DMARDs or targeted synthetic DMARDs. Steroid use remained relatively high at 86.2% among the subjects.

Evaluation of treatment responses using both DAS-28 with C-reactive protein (DAS-28 CRP) and DAS-28 ESR revealed that a substantial portion of patients still exhibited moderate disease activity (43.6-48.9%). Within the RA treatment program at RSCM, the proportion of patients achieving therapy target was 34% and 41.5%, according to DAS-28 CRP and DAS-28 ESR, respectively. Notably, most patients (45.7%) started DMARD therapy more than 2 years after the onset of symptoms.

A comparison of characteristics between subjects who achieved the therapy target and those who did not is presented in Table 2. The target-achieving group showed a higher percentage of MTX therapy (92.3%) compared to the non-achieving group (87.3%), although this difference was not statistically significant. Quality of life, as assessed by the HAQ, was observed to be significantly higher among the target-achieving group (lower HAQ scores) compared to the non-achieving group.

4. Discussion

In this study, it was observed that 93.6% of the research subjects were female, and a significant majority were not formally employed, with most of them being housewives. This female predominance aligns with the findings from previous studies on RA in Indonesia, such as the study by Darmawan et al., as well as a multinational Asia-Pacific study by Xing et al., reporting female proportion of 72.7% and 83.2%, respectively.[5,6] A similar gender distribution trend has also been documented in a study by Myasoedova et al. in the United States, in which females comprised 67-70% of the total RA cases.[7] These findings highlight the possible role of hormones, particularly estrogen, in the pathophysiology of RA development.[8]

With regards to employment status, this study reveals that most of the subjects were not engaged in formal employment (64.9%). This could be attributed to the cultural norms in Indonesia, where many married adult women typically assume the role of housewives. Alternatively, this finding might result from the diminishing physical activity and reduced functional status caused by the chronic progression of RA, potentially resulting in compromised work performance, and consequently, prompting patients to withdraw from work.

Several studies have also reported the impact of RA on work ability and performance of daily activities. A study conducted in the Netherlands by Vilsteren et al.[9] examined the effects of RA on work productivity. The findings of this research indicated a significant relationship between DAS-28 ESR scores and a decrease in the number of working hours, with an average loss of 4 productive working hours every 2 weeks per patient. Workers experiencing mental distress due to physical limitations resulting from RA also tended to experience greater loss of work hours.[9] Another study investigating the relationship between RA and work productivity demonstrated a significant and strong correlation between HAQ scores and workplace absenteeism ($r = 0.83$, $p < 0.001$), reduced productivity ($r = 0.942$, $p < 0.001$), and decreased daily activities ($r = 0.84$, $p < 0.001$).[10] This shows that as the quality of life of RA patients decreases, as indicated by higher HAQ scores, their work performance also declines. These broader consequences of RA warrant further investigation through longitudinal studies.

The disabling nature of RA was also demonstrated in the results of our study, in which HAQ scores were found to be significantly higher in the non-achieving group, indicating a decline in patients' functional status. This finding closely aligns with the results of a study conducted in Pakistan which revealed that disease activity was strongly correlated with functional status, in which patients experiencing moderate to high disease activity exhibited markedly higher HAQ scores than those with low disease activity or in remission.[11]

Table 1. Characteristics of subjects

Variables	N (%)	Mean (± SD) / Median (range)
Age (years)		51.24 (± 13.00)
Gender		
Male	6 (6.4)	
Female	88 (93.6)	
Body weight (kg)		59.00 (36-87)
Height (cm)		155.00 (130-173)
Body mass index (BMI)		23.84 (15.81-42.60)
Underweight	3 (3.2)	
Normal	59 (62.8)	
Overweight/obese	32 (34.0)	
Education level		
Below high school	1 (1.1)	
High school or equivalent	63 (67.0)	
Bachelor	30 (31.9)	
Employment status		
Not formally employed	61 (64.9)	
Part-time worker	5 (5.3)	
Full-time worker	23 (24.5)	
Retired	5 (5.3)	
Family disease history		
RA history present	20 (21.3)	
RA history absent	74 (78.7)	
Extraarticular manifestation		
Present	31 (33.0)	
Absent	63 (67.0)	
Comorbidities		
Present	60 (63.8)	
Absent	34 (36.2)	
Smoking history		
Present	11 (11.7)	
Absent	83 (88.3)	
DMARD use		
MTX (monotherapy or in combination)	84 (89.4)	
SSZ (monotherapy or in combination)	22 (23.4)	
MTX only	68 (72.3)	
SSZ only	10 (10.6)	
Combination of MTX + SSZ	7 (7.4)	
Combination of MTX + HCQ	1 (1.1)	
Combination of MTX + LEF	2 (2.1)	
Combination of MTX + CSA + chloroquine	1 (1.1)	
Combination of MTX + SSZ + LEF	3 (3.2)	
Combination of MTX + SSZ + CSA	1 (1.1)	
Combination of MTX + SSZ + HCQ	1 (1.1)	
Duration from symptoms onset to DMARD initiation		22.50 (0-579)
0-6 months	28 (29.8)	
7-12 months	10 (10.6)	
13-24 months	13 (13.8)	
>24 months	43 (45.7)	
Duration of treatment		22.50 (0-166)
0-6 months	19 (20.2)	
7-12 months	12 (12.8)	
13-24 months	20 (21.3)	
>24 months	43 (45.7)	
Steroid use		
On steroid use	81 (86.2)	
Not on steroid use	13 (13.8)	
Rheumatoid factor		60 (6-598)
Positive (>15.9)	62 (66.0)	
Negative (≤15.9)	24 (25.5)	
Not measured	8 (8.5)	
ESR		40 (2-126)
CRP		3.90 (0.18-54.70)
Patient pain VAS		3.00 (0-8)
Mild (0-3)	55 (58.5)	
Moderate (4-6)	32 (34.0)	
Severe (7-10)	7 (7.4)	
Patient global VAS		2.00 (0-9)
Mild (0-3)	68 (72.3)	
Moderate (4-6)	21 (22.3)	
Severe (7-10)	5 (5.3)	
Patient fatigue VAS		0.00 (0-6)
Mild (0-3)	82 (87.2)	
Moderate (4-6)	12 (12.8)	
Severe (7-10)	0 (0)	
Physician global VAS		2.00 (0-9)
Mild (0-3)	68 (72.3)	
Moderate (4-6)	21 (22.3)	
Severe (7-10)	5 (5.3)	
HAQ scores		0.17 (0.00-2.79)
DAS-28 ESR		3.66 (± 1.03)
Remission	13 (13.8)	
Low disease activity	26 (27.7)	
Moderate disease activity	46 (48.9)	
Severe disease activity	9 (9.6)	
Target achieved (remission-low)	39 (41.5)	
Target not achieved (moderate-severe)	55 (58.5)	
DAS-28 CRP		3.36 (± 1.11)
Remission	13 (13.8)	
Low disease activity	19 (20.2)	
Moderate disease activity	41 (43.6)	
Severe disease activity	21 (22.3)	
Target achieved (remission-low)	32 (34.0)	
Target not achieved (moderate-severe)	62 (66.0)	

Abbreviation: BMI: body mass index, CRP: C-reactive protein, CSA: cyclosporine, DMARD: disease-modifying antirheumatic drug, ESR: erythrocyte sedimentation rate, HAQ: Health Assessment Questionnaire, HCQ: hydroxychloroquine, LEF: leflunomide, MTX: methotrexate, RA: rheumatoid arthritis, SD: standard deviation, SSZ: sulfasalazine, VAS: visual analogue scale

Table 2. Comparative analysis of subject characteristics based on achievement of therapy target as evaluated by DAS-28 ESR

Variables	Target-achieving group (n = 39)		Non-achieving group (n = 55)		p-value
	N (%)	Mean (± SD) / Median (range)	N (%)	Mean (± SD) / Median (range)	
Age (years)		53.84 (± 12.80)		49.40 (± 12.94)	
Gender					1.000*
Male	2 (5.1)		4 (7.3)		
Female	37 (94.9)		51 (92.7)		
Body weight (kg)		60.00 (36-85)		57.00 (41-87)	
Height (cm)		155.00 (143-172)		156.00 (130-173)	
Body mass index (BMI)		24.56 (16.22-35.56)		23.56 (15.81-42.60)	
Underweight	1 (2.6)		2 (3.6)		0.946
Normal	25 (64.1)		34 (61.8)		
Overweight/obese	13 (33.3)		19 (34.5)		
Education level					0.191
Below high school	0 (0)		1 (1.8)		
High school or equivalent	30 (76.9)		33 (60.0)		
Bachelor	9 (23.1)		21 (38.2)		
Employment status					0.647
Not formally employed	28 (71.8)		33 (60.0)		
Part-time worker	2 (5.1)		3 (5.5)		
Full-time worker	7 (17.9)		16 (29.1)		
Retired	2 (5.1)		3 (5.5)		
Family disease history					0.613*
RA history present	7 (17.9)		13 (23.6)		
RA history absent	32 (82.1)		42 (76.4)		
Extraarticular manifestation					0.379*
Present	15 (38.5)		16 (29.1)		
Absent	24 (61.5)		39 (70.9)		
Comorbidities					0.085*
Present	29 (74.4)		31 (56.4)		
Absent	10 (25.6)		24 (43.6)		
Smoking history					1.000*
Present	4 (10.3)		7 (12.7)		
Absent	35 (89.7)		48 (87.3)		
DMARD use					
Use of MTX	36 (92.3)		48 (87.3)		0.515*
Use of SSZ	4 (10.3)		18 (32.7)		**0.013***
Duration from symptoms onset to DMARD initiation		15.00 (0-579)		24.00 (0-424)	
0-6 months	15 (38.5)		13 (23.6)		0.406
7-12 months	3 (7.7)		7 (12.7)		
13-24 months	4 (10.3)		9 (16.4)		
>24 months	17 (43.6)		26 (47.3)		
Duration of treatment		28.00 (1-166)		18.00 (0-119)	
0-6 months	6 (15.4)		13 (23.6)		0.558
7-12 months	4 (10.3)		8 (14.5)		
13-24 months	8 (20.5)		12 (21.8)		
>24 months	21 (53.8)		22 (40.0)		
Rheumatoid factor		60.00 (6-598)		60.00 (7-567)	0.965†
Positive (>15.9)	27 (69.2)		35 (63.6)		0.467
Negative (≤15.9)	8 (20.5)		16 (29.1)		
Not measured	4 (10.3)		4 (7.3)		
ESR		40.00 (15-79)		43.00 (2-126)	0.659†
CRP		4.50 (0.20-29.00)		3.80 (0.18-54.70)	0.779†
HAQ scores		0.06 (0.00-2.79)		0.25 (0.00-1.17)	**0.000†**

Abbreviation: BMI: body mass index, CRP: C-reactive protein, DMARD: disease-modifying antirheumatic drug, ESR: erythrocyte sedimentation rate, HAQ: Health Assessment Questionnaire, MTX: methotrexate, RA: rheumatoid arthritis, SD: standard deviation, SSZ: sulfasalazine, VAS: visual analogue scale

*: Fisher's exact test

†: Mann-Whitney test

Furthermore, in a study by Alemao et al., improved physical functioning was also observed in subjects who achieved therapy target measures, as opposed to those who did not.[12] When joints affected by RA are actively inflamed, patients frequently report an increased need for rest, decreased mobility, and a preference for activities that exert less strain on their joints. Consequently, these factors can compromise their ability to perform routine daily activities.[11,13] Considering that a significant proportion of our study subjects were housewives, difficulties in performing daily household chores would significantly affect their functional status, and hence, their overall quality of life.

This study also revealed that nearly all subjects (98.9%) completed at least high school or equivalent formal education. This finding serves as a favourable factor for a comprehensive RA management program, particularly to ensure that the patients understand the provided education. Education levels are also expected to impact patient adherence to planned therapy programs. However, in this study, no significant association was found between education level and patient treatment response. This might be attributed to the uneven distribution of subjects' educational background, with a very limited proportion having an education level below high school.

Regarding the duration between symptom onset and the first initiation of DMARDs, it was found that a majority of patients initiated DMARD therapy more than 2 years after the onset of symptoms (45.7%). This is a concerning issue which requires attention, given that DMARD is the main component of RA management to control disease activity, ideally administered within the first 6 months of symptom onset. This delay may result from delayed RA diagnosis or difficulties in accessing DMARDs. Diagnosis delay may arise from difficulties in referring patients to adequate healthcare facilities, limited availability of laboratory tests for diagnosis confirmation, lack of primary healthcare physicians' ability to diagnose RA, as well as a lack of knowledge and awareness about RA among the general population. On the other hand, difficulties in accessing DMARD may arise from barriers such as unavailability of medications in rural areas, financial constraints, or the presence of other medical issues contraindicating DMARD use.

In this study, it was observed that a significant proportion of patients received methotrexate as their primary DMARD, which is currently regarded as the anchor drug of RA. This aligns with various national and international recommendations. Another notable finding is that most of the subjects, both in the target-achieving and non-achieving group, were still using corticosteroids (86.2%). This indicates that the use of DMARDs as glucocorticoid-sparing agents is still not optimal. Additionally, in terms of disease activity, the proportion of patients achieving remission remains relatively low (13.8%), in comparison with the remission rates among RA patients in the Asia-Pacific region, which stands at 35.5%.[5] This could potentially be attributed to delays in initiating DMARD therapy due to delayed healthcare-seeking behavior, delayed diagnosis, delayed DMARD initiation decisions, or delays in adjusting DMARD dosages and types to achieve treatment targets. Delay in DMARD therapy has been shown to impact treatment responses, including conventional DMARDs.[14,15]

Furthermore, another significant contributor to the failure in achieving treatment targets may be the absence of subjects receiving biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) due to cost barriers. In this study, 17.1% subjects received combined conventional DMARD therapy, which, as per current recommendation, should ideally involve bDMARDs or tsDMARDs.2 By comparison, in other Asian countries with better DMARD access such as Japan and Singapore, the remission rate reached 48.2% and 34.9%, respectively.[5] A seven-year cohort study in France found that 32.1% of patients achieved remission in the beginning of the study, which then increased to 57.7% after a 7-year therapy follow-up. The utilization of bDMARDs, as well as the combination of biological and

conventional DMARDs, were found to be significantly related to disease remission ($p < 0.001$ and $p < 0.02$) and predicted remission in RA patients.[16] Another review by Chatzidionysiou et al.[17] explored randomized controlled trials comparing remission percentage between groups using a combination of methotrexate and bDMARD or tsDMARD versus groups using methotrexate as monotherapy. The results demonstrated that combination therapy achieved higher remission rates than the monotherapy group.[17] Consequently, there is a discrepancy in target achievement rates when compared to countries with access to all types of DMARDs. Therefore, efforts should be made to improve access to treatment using biological and tsDMARDs.

5. Conclusion

Based on this study, the achievement of RA therapy target at RSCM was 41.5%, with 13.8% achieving remission. Further research can be conducted to evaluate the factors that may influence the achievement of RA therapy targets.

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