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Differences of Clinical Disease Activity Index (CDAI) in Rheumatoid Arthritis Patients Towards the Use of Disease Modifying Anti Rheumatic Drugs (DMARD)

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ABSTRACT
Rheumatoid arthritis is an autoimmune disease commonly associated with progressive disability and systemic complications. Rheumatoid arthritis is characterized by inflammation and synovial hyperplasia, production of autoantibodies, and destruction of bone and cartilage. One of the assessments of rheumatoid arthritis disease activity is Clinical Disease Activity Index (CDAI). Rheumatoid arthritis can be prevented with a right therapy. One of the main therapies for rheumatoid arthritis is Disease Modifying Antirheumatic Drugs (DMARD). This study aims to determine the patient's sociodemographic characteristics, to see the pattern of drug use, and to determine the difference in the CDAI value before and after medication is given. This research is a descriptive and analytic study, with a retrospective approach. There were 61 patients who entered the inclusion criteria. The results showed that the most rheumatoid arthritis patients who received DMARD therapy were women (96.72%), among which aged 46-55 years (31.1%). From these women, 49.2% graduated from high schools and 45.9% were housewives . In the pattern of DMARD use, the presentation of DMARD monotherapy was 11.5%, the combination of DMARD and corticosteroid was 21.3%, the combination of DMARD and NSAID was 4.9%, and the combination of DMARD, corticosteroid, and NSAID was 62.3%. The highest DMARD use was methotrexate with a percentage of 62.3%. The findings conclude that there is a significant difference in the value of CDAI before and after DMARD was given in rheumatoid arthritis patients at Dr. M. Djamil Padang hospital, both on the use of DMARD monotherapy, combination of DMARD and corticosteroid, combination of DMARD and NSAID, and combination of DMARD, corticosteroid and NSAID. The average CDAI value after DMARD therapy was smaller than before treatment.

Keywords: *rheumatoid arthritis, therapy, DMARD, CDAI.*

1. INTRODUCTION

Rheumatoid Arthritis (RA) is an autoimmune disease commonly associated with progressive disability and systemic complications. The exact beginning of the development of RA is not known, but there is a theory that this disease starts from interactions by the environment that cause gene modification so that gene susceptibility occurs. This triggers a loss of tolerance to self-proteins containing citrulline residues, produced by post-translational modifications. This anticitrullinated response is found in the T-cell and B-cell compartments and begins in the secondary lymphoid tissue or bone marrow. Then localization of the inflammatory response occurs in the joint which may involve other microvascular, neurological, biomechanical, or tissue-specific pathways. Causes synovitis that over time leads to systemic disorders that form the rheumatoid arthritis syndrome [1].

Based on data from *Riset Kesehatan Dasar* (translated Basic Health Research) in 2018, women suffer more from this disease with the percentage of 8.5%, compared to men (6.1%). These data also show that most patients are over 75 years old (18.9%) and 7.8% of them live in rural areas [2]. RA is treated using corticosteroids, nonsteroidal anti-inflammatory drugs, and Disease Modifying Antirheumatic Drugs (DMARD) such as methotrexate, and rituximab and tocilizumab which are biologic DMARD. Treatment can be done by administering a single drug or a combination of two or three drugs. Treatment of RA has the goal of controlling symptoms and disease activity [3].

In rheumatoid arthritis, the assessment of disease activity can be assessed in several ways, one of which is the Clinical Disease Activity Index (CDAI). Assessment of disease activity is very important, because RA treatment decisions are based on disease activity [4]. The CDAI is one of the combined assessments of RA disease and is based on the

simple summation of the number of swollen and painful joints (28 joints) together with the patient's and physician's global assessment on the VAS (0-10 cm) scale. The main advantage of using CDAI is that it can be used anywhere and anytime for the assessment of disease activity in RA patients [5]. Research conducted by Savitri (2019) at Dr. Hasan Sadikin Hospital showed that the use of DMARD monotherapy, namely methotrexate, gave better results even though the therapy that was often used was methylprednisolone monotherapy or combination. This study uses the Disease Activity Score-28 (DAS28) as the parameter [3].

In rheumatoid arthritis therapy patients who use Disease Modifying Anti Rheumatoid Drugs (DMARD) the effectiveness of drugs according to the choice of using DMARD as monotherapy or combination is still confusing, and in Indonesia there has been no study that has looked at the effect of RA treatment on the CDAI. Therefore, this study was conducted to discuss the differences in the CDAI in Rheumatoid Arthritis patients against the administering of DMARD in outpatient polyclinics specifically for rheumatology at Dr. M. Djamil Padang Hospital in 2016 - 2020.

2. METHODS

This research was carried out at the medical record installation of Dr. M. Djamil Padang Hospital. This study has ethical approval issued by the Health Research Ethics Committee of Dr. M.Djamil Padang Hospital with No: 124/KEPK/2021. This type of research is descriptive and analytic, with a retrospective approach. Purposive sampling method was selected as all data that met the criteria were sampled. Data were obtained from the medical records of outpatient rheumatoid arthritis patients at the Special Polyclinic of Rheumatology at Dr. M. Djamil Padang Hospital during the period of 2016 - 2020. The selection of patients was based on the inclusion criteria, namely rheumatoid arthritis outpatients at the Special Polyclinic for Rheumatology at Dr. M. Djamil Padang Hospital, who are in productive age, the elderly patients who receive DMARD therapy, and those who do regular and timely follow-up every month. The data taken from the patient's medical record is the patient's characteristic data in the form of the patient's name, gender, age, educational status, and job; DMARD drug data used by the patient; and clinical disease data such as the number of painful joints, the number of swollen joints, the global assessment of pain from the doctor and the global assessment of pain from the patient.

The threshold Values for Rheumatoid Arthritis Disease were depicted in **Table 1**, and for the initial condition, CDAI value patient's must be >2.8 or the disease activity is not in remission. The number of patient visits is at least 2-3 times, depending on what DMARD drug is used, because the duration of DMARD effect depends on the drug intake, the average duration is 1-2 months.

The CDAI value taken is the value listed in the patient's medical record. The joints assessed in the CDAI are the shoulder, elbow, wrist, metacarpophalangeal (MCP), proximal interphalangeal (PIP), and knee. The CDAI has the formula [6]:

CDAI= SJC28 + TJC28 + patient global health (VAS; 0–10) + physician global (VAS; 0–10)

Descriptions: SJC28 = *28-swollen-joint-count*, TJC28 = *28-tender-joint count* VAS, visual analogue scale.

Table 1. Threshold Values for Rheumatoid Arthritis Disease

Disease Activity	CDAI value
Remission	≤ 2.8
Mild	< 10
Moderate	< 22
High	≥ 22

Exclusion criteria for patients were medical records of outpatients not patients with rheumatoid arthritis, new patients and incomplete medical records of outpatients with rheumatoid arthritis. Statistical analysis was performed with IBM SPSS 26 using the Wilcoxon test to see the results of therapy by comparing the CDAI values before and after using DMARD (monotherapy or combination).

the patients in the initial data, none were in the remission stage, 11 patients were in the mild stage, 43 patients were in the moderate stage, and 7 patients were in the high stage. Sociodemographic characteristics of Rheumatoid Arthritis patients were despicted in **Table 2**. The results had the similiarity with the results obtained by Savitri (2018) in his research [3].

3. RESULTS AND DISCUSSION

The results showed that there were far more patients with RA in female patients than in male patients. The age most suffering from RA is in the early elderly category (46-55 years) with a percentage of 96.72%. Based on the level of education, patients who have the last high school education are the most (49.2%). In the employment status, patients who are housewives are the most number (45.9%). Of all

The high number of women is influenced by hormonal disorders. When women are going through menopause, the hormone estrogen decreases and this is a condition that

triggers autoimmune disorders in the body [3]. The hormone estrogen also inhibits osteoclast regeneration [7]. Old age and a bad lifestyle are also very influential, such as smoking, drinking coffee, and weight gain [6]. Education level is one of the factors that influence patients to make decisions in treating their disease. The higher a person's knowledge, the easier it is for them to receive information, and the higher the awareness of health. Thus, the desire for treatment will be even greater [8]. **Table 2** shows that housewives are professions that use the most physical activity compared to other occupations. According to Ilar (2018), the higher a person's physical activity, the higher the risk of rheumatoid arthritis [9].

Table 2. Sociodemographic characteristics of Rheumatoid Arthritis patients

Characteristic Data	Category	n	%
Gender	Man	2	3.28
	Woman	59	96.72
Age	20 - 24	4	6.6
	25 - 34	12	19.7
	35 - 44	15	24.6
	45 - 54	19	31.1
	55 - 64	8	13.1
	>65	3	4.9
Level of Education	Didn't Finish Elementary School	3	4.9
	Elementary School	4	6.6
	Junior High School	2	3.3
	Senior High School	30	49.2
	Diploma	1	1.6
	Bachelor	21	34.4
Job Status	Housewife	28	45.9
	Student	3	4.9
	Government Employees	13	21.3
	Private Employees	6	9.8
	Entrepreneur	2	3.3
	Etc	9	14.8

When using DMARD in the outpatient polyclinic in rheumatology section of Dr. M. Djamil Padang Hospital in the period of 2016 - 2020, it is known that methotrexate is the most widely taken. There are monotherapy and combination DMARD with other drugs. In monotherapy, the DMARD used is methotrexate. In combination, DMARD are combined with corticosteroid and NSAID or a combination of both. Percentage and number of people that use rheumatoid arthritis in Dr. M. Djamil Padang Hospital drugs were depicted in **Figure 1.**

The dose of methotrexate given was 7.5-15 mg/week, for cyclosporine 2x25 mg, leflunomide 1x20mg/day, azathioprine 2x25mg/day, and sulfasalazine 1x500mg/day. Among these doses that are not appropriate are cyclosporine and sulfasalazine, where the exact dose is for cyclosporine 2.5-5mg/kg and for sulfasalazine is 2x500mg/day [4]. If the dose given is not appropriate, then the desired therapy will not be achieved. All drugs given are in tablet and oral route of administration. Methotrexate has a mechanism of reducing polymorphonuclear chemotaxis and influencing DNA synthesis, cyclosporine functions to block the synthesis of IL-1 and IL-2, leflunomide works by inhibiting the enzyme dihydroorotate dehydrogenase so that auto-reactive T lymphocyte cell division is inhibited, azathioprine mechanism is to inhibit the synthesis of purines and sulfasalazine works by inhibiting polymorphonuclear migration and angiogenesis [4,10].

In DMARD monotherapy, the dose of methotrexate used is 10 mg/week. Corticosteroids used with DMARD are methyl prednisolone 4 mg, and NSAIDs used are diclofenac sodium 50 mg and ibuprofen 200-400 mg. The most common pattern of DMARD use is a combination of DMARD, corticosteroid, and NSAID. The combination of RA drugs with corticosteroids and NSAIDs aims to reduce the symptoms that appear, but the use of corticosteroids and NSAIDs must use the lowest effective dose possible, and also should not be combined with each other, because it will only increase side effects and do not increase the therapeutic effect [4]. That's why the combination of DMARD, corticosteroid, and NSAID performed at M. Djamil Hospital is not appropriate. Not only that, the study also found that there was a combination of DMARD with 2 NSAID drugs. According to the management of RA, the use of 2 NSAIDs is not recommended, because it will not increase the therapeutic effect and only increase side effects [4]. In a study conducted by Savitri (2019) at Hasan Sadikin Hospital, there was no combination of drugs between DMARD, corticosteroid, and NSAID. The only use of the drug is methotrexate monotherapy; methotrexate with methyl prednisolone (corticosteroid); methotrexate with other DMARD; and methotrexate, methyl prednisolone, other DMARD [3].

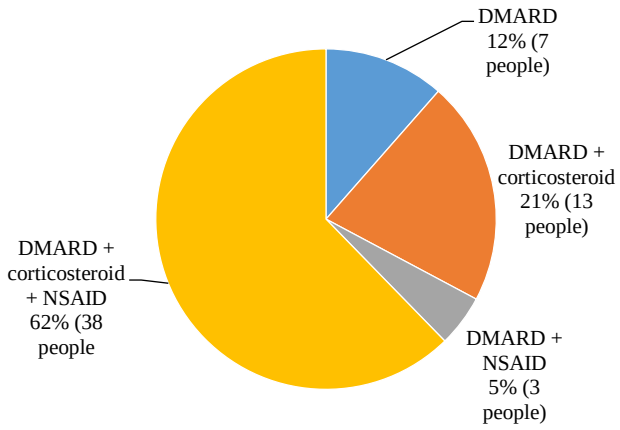

Figure 1. Distribution of drug use in rheumatoid arthritis patients

RA patients who used DMARD in total were 61 people, with 7 people using monotherapy, 13 people using a combination of DMARD and corticosteroid, 3 people using a combination of DMARD and NSAID, and 38 people using a combination of DMARD, corticosteroid, and NSAID. In the analytical test using the Wilcoxon test, it was found that all p values in each drug category were $p < 0.05$, which means that there was a significant difference in CDAI values before and after DMARD administration. The data shows that the CDAI value after using DMARD is smaller than before using DMARD, which means that there is a decrease in the level of disease activity, although not all of those who experience a decrease in the CDAI value experience a decrease in the level of disease activity (see **Table 4**).

From the results of the study, it can be seen that there were 7 patients (12%) who received DMARD monotherapy, and the drug used was methotrexate. All of these patients received DMARD at their first visit when the doctor had already confirmed the diagnosis that this patient had rheumatoid arthritis. The dose given is 10 mg/week. From the data, it can be seen that the average patient experienced a decrease in CDAI value after one month of receiving this therapy. In statistical analysis using Wilcoxon, $p<0.05$ was obtained. This, means that there is a significant difference in CDAI values before and after drug administration. From the data, it can also be seen that the CDAI value after DMARD administration was smaller than before.

The guidelines in Dipiro (2017) recommend DMARD monotherapy (methotrexate is expected) in new patients with rheumatoid arthritis. If patients taking this drug have increased disease activity (moderate-high), it is recommended to change to another type of DMARD, or do a combination with another DMARD. At M. Djamil Hospital Padang, DMARD replacement was performed, or DMARD was combined with corticosteroids or NSAID and not with other DMARD [10]. DMARD combination drug with corticosteroid was used by 13 patients (21%). A total of 8 patients used a combination of methotrexate (10-15 mg/week) and methyl prednisolone (4 mg dose), 4 patients used a combination of cyclosporine (2x25 mg dose) and methyl prednisolone (4 mg), and 1 patient used a combination of sulfasalazine (1x500 mg) and methyl prednisolone (4 mg). In statistical analysis using Wilcoxon, obtained $p<0.05$, which means that there is a significant difference in CDAI values before and after drug administration.

There were 3 patients (4.9%) who used DMARD and NSAID combination drugs. A total of 2 patients used a combination drug of leflunomide (1x20mg) with diclofenac sodium (1-2x50mg), and 1 patient used a combination drug of cyclosporine (2x25mg), diclofenac sodium (1x50mg), and ibuprofen (1x400mg). From the three samples, it can be seen that all three experienced a decrease in the CDAI value, but only 2 experienced a moderate decrease in disease activity while 1 remained constant. From this we can see that on average there is a difference in CDAI values before and after drug administration. From the data, it can also be seen that the CDAI value after DMARD administration was smaller than before DMARD administration in rheumatoid arthritis patients.

Table 4. Wilcoxon test data on CDAI before and after DMARD therapy

NO	DATA		n	Median	Minimum - Maximum	*P* value
1	All	Before administering medication	61	12	8-39	0,000
		After administering medication	61	8	0-34	
2	DMARD	Before administering medication	7	8	8-20	0,027
		After administering medication	7	8	0-8	
3	DMARD + Corticosteroid	Before administering medication	13	12	9-39	0,002
		After administering medication	13	8	6-34	
4	DMARD + Corticosteroid + NSAID	Before administering medication	38	12	8-31	0,000
		After administering medication	38	8	1-30	

In the combination of DMARD, corticosteroid, and NSAID drugs, 38 patients (62.3%) used it. This combination is divided into 2, there is a combination of 3 drugs and a combination of 4 drugs (there are 2 NSAIDs). In statistical analysis using Wilcoxon, obtained $p<0.05$, which means that there is a significant difference in CDAI values before and after drug administration. From the data, it can also be seen that the CDAI value after DMARD administration was smaller than before DMARD administration in rheumatoid arthritis patients.

In the study it was found that in rheumatoid arthritis patients there was clinical improvement after drug administration. The VAS scale for doctors and patients, on average, showed a significant decrease. Similarly, the number of swollen joints count (SJC), after being given therapy, the average swollen joints reduced or disappeared altogether. For the number of painful joints count (TJC) on average there was no change, and the number was constant, but the degree of pain decreased. This is seen from the degree of pain (VAS scale) of doctors and patients described above. It is known that the DMARD given has the potential to reduce joint damage, maintain joint integrity and function, not only that NSAIDs and corticosteroids are used as adjuvant therapy to reduce symptoms, such as pain that occurs [4].

In pasha's research (2017) it was found that the CDAI results reflect the results of the DAS-28 [11]. in Savitri's (2018) study using DAS-28 it was found that metrotrexate gave better results even though the therapy that was often used was methylprednisolone monotherapy or combination [3]. In this study it was found that there were positive and good results on the use of DMARD.

4. CONCLUSION

This study found that there was a significant difference in CDAI values before and after DMARD administration. Additionally, the CDAI value after is smaller than before, which means that there is a decrease in the level of disease activity. The results also indicate that the combination of DMARDs, corticosteroids, and NSAIDs is the most widely used therapy in outpatients at the Specialized Rheumatology Polyclinic at Dr. M. Djamil Padang Hospital 2016-2020.

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