Treatment of Rheumatoid Arthritis with Methotrexate only or a Combination of Methotrexate and Hydroxychloroquine

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Abstract

Background: Rheumatoid arthritis (RA) is an autoimmune disease that causes significant morbidity in most patients and also premature mortality in some. To prevent this, therapeutic approaches call for the early treatment of RA by using disease-modifying antirheumatic drugs (DMARDSs), either as single therapy or combination therapy. Although in the previous decade DMARDs were rarely used as combination, now they are used widely to treat RA. The objective of this study was to compare the effectiveness of methotrexate (MTX) on its own and the combination of MTX & hydroxychloroquine (HCQ) in RA patients.

Methods: An analytic retrospective cohort study was conducted from May 2014 to October 2014, on 46 patients with RA at the rheumatology clinic of Dr. Hasan Sadikin General Hospital Bandung in the period from January 2009 to October 2014, who were taking MTX or MTX & HCQ for at least 1 year. The secondary data obtained from these patients' medical record were then analyzed using the independent t-test and Mann-Whitney test.

Results: The study showed that female patients dominated than male patients which were 93.48%. The mean change in disease activity measures was not significant for any of the parameter (p-value for SJC = 0.337; TJC = 0.676; ESR = 0.780). In addition, the comparisons of the disease activity score (DAS 28) before and after therapy were not significant (p-value = 0.584).

Conclusions: There is no difference in the effectiveness of DMARD monotherapy with MTX and combination therapy with MTX & HCQ in RA patients. **[AMJ.2016;3(3):446–51]**

Keywords: DAS 28, DMARDs, hydroxychloroquine, methotrexate, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease[1] and also a chronic systemic inflammatory disorder[1,2] that causes joint swelling, joint tenderness, and destruction of synovial joints.[1] Even though the etiology seems to be unknown, however, there are certain risk factors said to be associated with RA, such as genetic and environmental factors.[3] Although RA affects people of all ages, its onset occurs between 30–55 years of age, with women more likely to suffer from RA compared to men.[4] Until today, there is no specific cure for RA. However, there are available certain drugs or medications to help decrease symptoms, reduce inflammation, and slow the progression of the disease.[5]

The treatment approach for RA has two main goals: first, the relief of symptoms (symptomatic treatment) and maintenance of function and second, the slowing of the tissue-damaging process (modifying treatment).[6] Disease-modifying antirheumatic drugs (DMARDs) have the capability to arrest or at least to control the disease process in RA by modifying the disease itself.[7] Disease-modifying antirheumatic drugs have the ability to reduce signs and symptoms, disability, impairment of quality of life, and progression of joint damage and hence; they interfere with the entire disease process. Disease-modifying antirheumatic drugs can be classified into two major groups: synthetic DMARDs (sDMARDs)

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and biologic DMARDs (bDMARDs).[8] The Disease Activity Score (DAS, DAS28) that is used to record disease activity and determine the therapeutic efficacy consists of four items; the number of swollen and tender joints (SJC, TJC), the visual analogue scale of patients' assessment of their general health (VAS-GH), and the erythrocyte sedimentation rate (ESR) in the first hour.[9] Early treatment with DMARDs has shown improved outcomes of signs and symptoms and also slower progression of damage to joints[10] by changing the course of RA itself.[11] Currently, MTX (methotrexate) is the most preferred synthetic DMARD (DMARD of first choice)[12] because many patients on MTX have good response and serious toxicities are rare.[13] However, not all patients have good treatment response with MTX monotherapy.[12] This study was conducted to compare the effectiveness of MTX on its own and the combination of MTX & HCQ in RA.

Methods

An analytic retrospective cohort study was conducted from August 2014 to October 2014 at the rheumatology clinic of Dr. Hasan Sadikin General Hospital Bandung. This study was conducted after it was approved by Ethical Clearance Committee of Dr. Hasan Sadikin General Hospital Bandung. The research population in this study was RA patients who came to the rheumatology clinic at Dr. Hasan Sadikin General Hospital Bandung. However, the samples of this study were new RA patients in the rheumatology clinic from January 2009 to October 2013 who had a follow-up minimum one year. The inclusion criteria for the study were RA patients aged 19–80 years old whose cases were being followed up at the rheumatology clinic. All RA patients with complete data in their medical records and patients who had not previously received a combination therapy with any of the medications were studied in this study. The exclusion criteria for the study were patients who had stage IV disease. A concurrent therapy with systemic corticosteroids was allowed if the dosage remained stable throughout the study period and the patient took ≤ 10 mg of prednisone (or its equivalent) per day.

Based on these criteria, 46 samples were obtained from a calculated sample size of 92 whereby 23 of them took MTX monotherapy and the other 23 took the combination therapy of MTX & HCQ. The starting dose for MTX was 7.5-10mg per week and was increased gradually depending on the patients' respsonse to therapy meanwhile the dosage of HCQ was 200mg per day. The type of study chosen to compare the effectiveness of the monotherapy and combination therapy was analytic retrospective cohort study. The response to treatment was studied in the 6th and 12th month. Variables of this study were type of DMARD therapy (monotherapy or combination therapy) and the disease activity

Table 1 Characteristics of Respondents according to Study Group*

Characteristics	MTX	MTX & HCQ	All Patients
No. of patients	23	23	46
Gender			
Male	2 (8.70%)	1 (4.35%)	3 (6.52%)
Female	21 (91.30%)	22 (95.65%)	43 (93.48%)
Age, years, mean (range)	44.1 (19–78)	43.8 (24–65)	44 (19–78)
19–28 years (n)	3	3	6
29–38 years (n)	5	6	11
39–48 years (n)	8	7	15
49–58 years (n)	3	5	8
59–68 years (n)	3	2	5
69–78 years (n)	1	0	1
Mean dosage of corticosteroids, mg/ day ± SD	5.4 ± 2.1	5.6 ± 1.9	5.5 ± 2.0

Note: * MTX = Methotrexate; HCQ = Hydroxychloroquine

Table 2 Initial Values for Disease Activity Measures by Treatment Group*

Parameters	MTX	MTX & HCQ
SJC (maximum 28)	2.52 ± 5.66	3.48 ± 4.22
TJC (maximum 28)	8.83 ± 7.42	9.57 ± 5.62
ESR (mm/h)	44.83 ± 34.49	53.57 ± 31.20

Note: * Values are the mean ± SD. MTX = Methotrexate; HCQ = Hydroxychloroquine; SJC = Swollen joint count; TJC = Tender joint count; ESR = Erythrocyte sedimentation rate

score, DAS28. The effectiveness of the therapy was seen based on the comparison of the DAS 28 before and after the DMARD therapy (after 12 months of therapy) whereby the DAS 28 of each patient was calculated using the online DAS 28 calculator for three variables (SJC, TJC, and ESR) at http://www.das-score.nl/das28/DAScalculators/dasculators.html and then categorized as follows: low (DAS28 ≤ 3.2), moderate (3.2 < DAS28 ≤ 5.1), or high (DAS28 > 5.1).

The data from the medical records were statistically analyzed using independent t-test for data that were normally distributed and Mann Whitney non-parametric test if there were anomalies in the data distribution. Statistical significance was considered when p ≤ 0.05. Analysis was performed by comparing the both treatment groups.

Results

Of the 46 patients in this study, 23 took MTX while the other 23 took MTX & HCQ. The distribution of sex, age, and daily corticosteroid usage were roughly balanced across the treatment groups (Table 1). The individual parameters of the disease activity measures were shown in Table 2, representing the findings at study entry. Both groups were roughly balanced in terms of these parameters in study entry. Table 3 showed the mean change in the individual parameters of the disease activity measures at the end of the study, by treatment group. The comparison on the effectiveness of monotherapy with MTX and combination therapy with MTX & HCQ based on DAS28 was shown in Table 4 whereby a p-value ≥ 0.05 was obtained indicating the insignificant results

Discussion

From the overall data obtained for the outpatients' medical record installation, there were a total of 213 patients who visited the rheumatology clinic from January 2009 to October 2014 whereby the total of female patients were 165 (77.5%) and male patients were 48 (22.5%). The incidence was a lot higher in females compared to males with a ratio of 3:1. In fact, this is true whereby other autoimmune diseases, RA has a higher occurrence in females compared to males with a ratio of 2–3:1. Meanwhile, studies from certain Latin American and African countries showed a considerably greater predominance of RA in females compared to males with a ratio of 6–8:1. Many theories have proposed the role of estrogens in this disease said that estrogens enhance the immune response by stimulating the production of tumor necrosis factor α (TNF–α) which is an important cytokine in the pathological process of RA.[2]

The average age of patients in this study was 44 years old and mostly (32.61%) were in the age range of 39–48 years old. Most of the studies conducted on RA in Europe showed that the average age of the patients is between 48.9–52.1 years.[14,15] Besides, a study by Alam et al.[16] in Bangladesh to compare the effectiveness of MTX against HCQ showed that

Table 3 Changes in Values for Disease Activity Measures by Treatment Group

Parameters	MTX	MTX & HCQ	P-value
SJC (maximum 28)	- 1.52 ± 4.73	- 2.22 ± 4.07	0.337**
TJC (maximum 28)	- 5.74 ± 7.37	- 6.57 ± 5.85	0.676*
ESR (mm/h)	- 15.61 ± 33.68	- 13.09 ± 26.74	0.780**

Note: * Mann Whitney test; ** Independent t-test . MTX = Methotrexate; HCQ = Hydroxychloroquine; SJC = Swollen joint count; TJC = Tender joint count; ESR = Erythrocyte sedimentation rate

Table 4 Comparison on the Effectiveness of Monotherapy with MTX and Combination Therapy with MTX & HCQ based on DAS28 *

Category of DAS 28 Score	Treatment Group				Total		P-value
	MTX		MTX & HCQ				
	f	%	f	%	f	%	
Before Treatment							
Low	0	0.00	1	100.00	1	100	
Moderate	17	58.62	12	41.38	29	100	
High	6	37.50	10	62.50	16	100	
After Treatment							
Low	9	60.00	6	40.00	15	100	0.584
Moderate	13	46.43	15	53.57	28	100	
High	1	33.33	2	66.67	3	100	

Note: * DAS 28 = Disease Activity Score 28; MTX = Methotexate; HCQ = Hydroxychloroquine; f = frequency

the average age of patients in their two study groups is 41.7 and 42.9 years old respectively. It was said that RA mostly occurs between 40–70 years old and it als occurs later in life for men.[2] This may be due to the fact that women begin to experience menopause around the fifth decade of life causing a decrease in their estrogen levels. Hence, it can be said that women are likely to suffer from RA when their estrogen level is still high, which is before 50 years old (average).

The changes in value for SJC and TJC at the end of this study were -1.5 and -5.7 for the MTX group and -2.2 and -6.6 for the combination therapy group, respectively. In a study conducted by O'Dell et al,[17] the mean changes in value for SJC and TJC after taking MTX & HCQ are -14.0 and -10.0, respectively, which are higher compared to the results in this study. However, it should be noted that the study conducted by O'Dell JR et al.[15] used the 38 joint count compared to the 28 joint count used in this study. This difference in joints count could be one of the reasons for the low changes in SJC and TJC values in this study.

Many research and studies have been conductedto determine the effectiveness of DMARDs. O' Dell JR et al.[17] conducted two different studies to determine the effectiveness of triple therapy against dual and monotherapy. In their first study, they demonstrated the superior efficacy of the triple combination therapy (MTX, HCQ, & sulfasalazine, SSZ) over both MTX on its own and the double combination of MTX & SSZ.[17] In their second study, they concluded that the efficacy of the triple combination of MTX, SSZ, & HCQ is superior to the double combination of MTX & SSZ and marginally superior to the double cobination of MTX & HCQ.[15] This is supported by the tREACH trial conducted by de Jong et al.[18] that concluded that therapy with a combination of DMARDs is better than MTX monotherapy.

In this study, it was showed that double therapy is similar in effectiveness to monotherapy. The results of this study contradict the results of previous studies. One of the main reasons is the small sample obtained in this study; larger samples increase the chance of finding a significant difference because they more reliably reflect the population mean. In this study, although the calculated sample size was 92, however, only 46 samples were obtained. Comparing to other studies, the sample size used was large (about 150–200 patients).[15]

It is not known why certain patients with RA respond to treatment better compared to others. A study by Anderson et al.[19], showed certain factors to answer this question and one of the factors is the disease duration. Their study showed that patients with longer disease duration have a poorer response to treatment compared to patients with shorter disease duration. In their study, they stated that there are indications that the biologic process of RA change early in the disease, so that patients may be less responsive to treatment over time. Other factors that were said to decrease response to treatment were female sex, prior DMARD use, and worse functional class. It was also stated that rheumatoid factor affects response to treatment.[19] In another study

by Radovits et al.[20], to find out the influence of age and gender on DAS28 in rheumatoid arthritis, they concluded that age and gender do not affect the DAS28 of RA patients. Due to the unavailable complete data in the medical record, this study could not conclude if these factors influence the response to treatment in RA.

It was concluded that there is no difference in the effectiveness of DMARD monotherapy with MTX and combination therapy with MTX & HCQ in RA patients.

The limitations of this study are some of the medical records were not available in the storage room where there are possibilities that the medical records are misplaced by the staffs of medical record. Besides, some of the medical records also do not have the complete or required data and, hence, cannot be used in this study.The number of the study sample can be one of the limitations of the study which a larger number of study sample can be used reflecting the population clearly. Lastly, time constraint is also one of the limitations with the tight academic schedules and short duration for data collection and analysis for this study.

Certain recommendations can be considered to improve this study. First and foremost is improving the management of medical record at rheumatology clinic of Dr. Hasan Sadikin General Hospital Bandung so that the data of the patients that are obtained from the medical record can be used and analyzed properly. Next a standardized medical form can be used so that physicians attending to patients at the rheumatology clinic will not forget or over look to fill up the relevant data in the medical record. Increasing the period of data collection is also suggested to enable the researcher to get more patients to meet the targeted sample size. Lastly, further studies about another DMARD therapy for RA should be conducted to get more information about the effectiveness of other DMARDs.

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