Proportion and Factors that Associate with Incidence of Hepatotoxicity in Rheumatoid Arthritis Patients Treated with Methotrexate in RSCM Year 2013–2015

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Abstract

Background Rheumatoid arhtirtis (RA) is a chronic autoimmune disease that mainly attacks joints. It may causes joint deformities which leads to lower quality of life of RA patients. RA is treated with metothrexate (MTX) which inhibiting disease progression. MTX is known for its hepatotoxicity side effect, which is described by an elevation of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) beyond the upper normal limit. Factors that may enhance hepatotoxicity are gender, age, cummulative dose of MTX, and duration therapy of MTX. Prevalence of hepatotoxicity caused by MTX therapy in RA patients in Indonesia is still unknown. The objective of this research is to know the proportion of hepatotoxicity and its associations with the factors that may enhance hepatotoxicity caused by MTX therapy in RA patients in RSCM.

Method Data about gender, age, cummulative dose and duration therapy of MTX are obtained from 115 RA patients' medical records.

Result Proportion of hepatotoxicity in RA patients treated with MTX in RSCM is 42.60%. Gender, age, cummulative dose and duration therapy of MTX do not significantly enhance hepatotoxicity ($p > 0.05$).

Conclusion In conclusion gender, age, cummulative dose and duration therapy of MTX do not have association with hepatotoxicity in RA patients treated with MTX.

Keywords: Rheumatoid Arthritis, Methotrexate, Hepatotoxicity

Introduction

Rheumatoid arthritis (RA) is an inflammatory disease which has large impacts on daily activities of its sufferers. Inflammation manifests as pain that causes joint immobility. American College of Rheumatology and European Leauge Against Rheumatism (ACR-EULAR) created a tool to help diagnose RA in 2010. After the diagnosis is set, patient would be treated with Disease Modifying Anti Rheumatic Drugs (DMRADs). The target of DMARDs therapy is inhibiting joint erosion and causing remission. Based on ACR guideline on management of RA in year 2015, the first line therapy for is methotrexate (MTX). MTX works by supressing cytokine release and lymphocyte proliferation that contributes to the progressivity of RA.[1-7]

Methotrexate is known to trigger liver dysfunction as side effect. Liver function is evaluated based on alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) serum titer. Elevation of liver enzyme above the upper limit indicates liver dysfunction. Based on study in India on 30 patients who were treated with MTX for 3 months, there was 25% elevation of AST above normal range.[8] Study in Israel on 119 patients who were treated with MTX showed 43% of RA patients have abnormal liver enzyme titer.[9] Study in Iran on 286 patients who were treated with MTX found that 23.7% of patients have experienced liver dysfunction.[10] Based on the previous studies, factors that suspected association with liver dysfuction are gender, age, MTX cumulative dose, and MTX duration therapy.[8-11]

There is not any study about proportion of liver dysfuction on RA patients who are treated with MTX in Indonesia. The purpose of this study is to know the proportion of liver dysfunction in patients who are treated with MTX, and to analyze the association between age, gender, MTX cumulative dose, MTX therapy duration with liver dysfunction incidence, so that clinicians will be more aware with MTX use in patients.

Methods

This study is a descriptive-analytic study with cross-sectional method. From the sample population, AST and ALT lab results, age, gender, MTX cumulative dose, and MTX duration therapy were obtained. The study was conducted in RSUPN Dr Cipto Mangunkusumo (RSCM) and RSCM Kencana, Jakarta for 11 months, from January to November 2016.

Data were obtained from patients' medical records unit RSCM and RSCM Kencana, which meet inclusion criteria and opposite of exclusion criteria. The inclusion criterias are patients who fulfill diagnosis criteria of based on ACR/EULAR 2010, received MTX therapy for minimum period of one month, and patients of RSCM and RSCM Kencana. The exclusion criterias are patients who have other comorbidities that can cause liver dysfunction.

Data were processed by SPSS software and analyzed with inferential statistic. Gender and liver function variables were analyzed with Fisher test. Age, MTX cumulative dose, and MTX therapy duration variables undergone sample normality test with Kolmogorov Smirnov test. If the data distribution were normal, unpaired T- test between age, MTX cumulative dose, and MTX duration therapy and liver function would be conducted. If not normal, the Mann-Whitney test would be done. From the Mann-Whitney test, p value showed data significance.

Result

From 115 samples who were obtained, all the samples were given MTX with minimum dosage of 7.5 mg each week for minimum duration of one month. Samples do not have any comorbidities that could result in liver dysfunction. Samples demographic datas are shown in Table 1.

Table 1. Samples Demographic Data

Variable	Result
Gender, frequency (%)	
Men	9 (7.83%)
Women	106 (92.17%)
Age (year)	53.55 (19.98−84.53)*
MTX cumulative dose (mg)	480.00 (25.00−3967.50)*
MTX duration therapy (week)	44.00 (4−226)*
AST titer, frequency (%)	
Normal	73 (63.48%)
1−2 times above normal	36 (31.30%)
>2 times above normal	6 (5.22%)
ALT titer, frequency (%)	
Normal	75 (65.22%)
1−2 times above normal	34 (29.56%)
>2 times above normal	6 (5.22%)
Liver dysfunction, frequency (%)	49 (42.60%)

*:not normally distributed data, data presented in median (range)

Association between gender and liver dysfunction

There is no significant difference between proportion of men and women (p>0.05) in group with liver dysfunction and without.

Table 2. Association between gender and liver dysfunction

Variables	Normal LFT	Disturbed LFT	P value
Women	63 (95.5)	43 (87.8)	0.167
Men	3 (4.5)	6 (12.2)	

LFT: Liver Function Test

Association between age and liver dysfunction

There is no significant association between age and liver dysfunction incidences (p>0.05).

Table 3. Association between age and liver dysfunction

	Liver function	Result	P score
Age	Normal	52.85 (19.98−84.53)*	0.46−0.23
	Disturbed	54.78 (23.56−72.75)*	

*:not normally distributed data, data presented in median (range)

Association between MTX cumulative dose and liver dysfunction

There is no significant association between MTX cumulative dose and liver dysfunction incidences (p>0.05).

Table 4. Association between MTX cumulative dose and liver dysfunction

	Liver function	Result	P score
MTX cumulative dose	Normal	378.75 (25.00−3337.50)*	0.23−0.115
	Disturbed	495.00 (50.00−3967.50)*	

*:not normally distributed data, data presented in median (range)

Association between MTX duration therapy and liver dysfunction

There is no significant association between MTX duration therapy and liver dysfunction incidences (p>0.05).

Table 5. Association between MTX duration and liver dysfunction

	Liver function	Result	P score
MTX duration therapy	Normal	43 (4−226)*	0.519−0.259
	Disturbed	44 (5−207)*	

*:not normally distributed data, data presented in median (range)

Discussion

Proportion of liver dysfuction in patients who are treated with MTX in RSCM and RSCM Kencana is 42.60%. The proportion of liver dysfunction in this study is higher than study conducted by Sotoudenamesh et al which has proportion of liver dysfunction 23.7%.[11] However, proportion of liver dysfunction in this study is suitable with other studies which conducted by Ede et al which stated that proportion of liver dysfunction is 53% and Bath et al which stated proportion of liver dysfunction is 15−50%. RA patients who are treated with chronic MTX experienced elevations in ALT and/or AST above the normal upper limit. About 5% of which experienced elevation until 2 times the normal range.[12] This study result has 5.22% samples who experienced AST and/or ALT 2 times normal range. In the literature review by Conway et al liver dysfunction incidence is higher than liver dysfunction incidence in this study, AST and/or ALT elevations above normal upper limit and those who elevated above two times normal range is 48.9% and 16.8% respectively.[13]

Variations of liver dysfunction proportion in other studies might be caused different definitions of liver dysfunction. In this study, liver dysfunction is described as ALT and or AST abnormal result while treated with MTX. Sotoudenamesh et al described liver dysfunction as two abnormal ALT and AST results in interval of 2 weeks.[10] Kremer et al described liver dysfunction based on liver hystology. The proportion differences also can be caused by different sample characteristics (ethnic and genetic variation).[10]

The time of laboratory test from last administration of MTX can also affect the liver enzyme titer. If the lab test were conducted after MTX administration, liver enzyme titer would be higher.[14]

Folic acid supplementation is known to decrease the frequency of liver enzyme elevation.[15] MTX hepatotoxicity mechanism is still unknown but allegedly result from the same mechanism of this drug mechanism of action. MTX causes inhibition of DNA and RNA synthesis in liver which result in damage and degeneration of liver cell. If the patients were given folic acid, DNA and RNA synthesis are not disturbed.[14, 16]

Epidemiologically, RA incidence is two to three times higher in women than in men. The reason behind it is still unknown but thought to be genetic factor that X linked and estrogen factor.[14] Studies by Amital et al and Parvin et al found women are more fragile to liver enzyme elevations.[8,9] Hoekstra et al study shown women are more prone to MTX treatment discontinuation.[15] However, in this study, gender and liver dysfunctions do not have any significant association. This study result is suitable to Sotoudenamesh et al study.[10]

Age median in this study is 52.8 years (19.98, 84.53) in group without liver dysfunction and 54.78 years (23.56, 72.75) in group with liver dysfuncton. There is no significant association between age and liver dysfunction incidence. This result is suitable to study by Sotoudenamesh et al, Hoekstra, and McKendry which also did not find any association between age and liver dysfunction in RA patients who are treated with MTX.[10,15]

Most of MTX would be eleminated from the body through kidney, meanwhile kidney function would degenerate as the age increased. If MTX titer in body high, the risk of hepatotoxicity is even higher. Therefore age is considered as risk factor for MTX hepatotoxicity. However, some studies showed different result from the theory. Study by Felson in 496 RA patients and Bologna in 469 RA patients did not find association between age, kidney function, and elevation of liver enzymes.[15] In this study, the researchers do not know about patients' kidney function.

In this study, there is no significant comparison between MTX cumulative dose in group with liver dysfunction and without liver dysfunction. MTX cumulative dose median in group with liver dysfunction is 495 mg, meanwhile in group without liver dysfunction is 378.75 mg. Even though there is no significant difference, MTX cumulative dose median in group with liver dysfunction is higher than cumulative dose median in group without liver dysfunction. In this study, MTX cumulative dose is lower than in other previous studies.

The result of this study is not suitable with studies which conducted by Sakthiswary et al and Sotoudenamesh et al which were acquired significant difference of MTX cumulative dose in group with liver dysfunction and without liver dysfunction.[10,17] According to the theory, incidences of hepatotoxicity are associated with increasing MTX dose. However, in various studies by West et al and Lanse et al also did not find any increasing risk of hepatotoxicity with increasing of MTX dose.[18]

Study by Bath et al showed significant association between MTX cumulative dose and liver dysfunction in RA patients treated with MTX once a day or every two days. However, in RA patients treated with MTX once a week, there is a weak association between MTX cumulative dose and hepatotoxicity. Liver dysfunction incidence is more associated with time interval between two MTX administrations than MTX cumulative dose. When the drug is administrated in one week interval, MTX titer in the body is not high enough to cause hepatotoxicity.[18] In this study, RA patients are treated with MTX weekly. No significant difference in MTX cumulative dose and liver dysfunction could be caused by time interval between two administrations. Studies by Parvin et al and Rau et al stated that liver enzymes elevations were transient and will normalized after decreasing of MTX dose, giving of folic acid, or even without changes in MTX dose. [8,19]

No significant difference between MTX cumulative dose and liver dysfunction incidence could be caused by MTX cumulative dose which are lower in this study than other previous studies. In this study, MTX cumulative dose median in group without liver dysfunction is 378.75 mg and group with liver dysfunction is 495 mg. Meanwhile in Sotoudenamesh et al, MTX cumulative dose mean in group without liver dysfuncton is 1707.3 mg with 45.2% of them were given MTX more than 1.5 g.[10] In the literature review by Kremer, hepatotoxicity incidence in RA patients who are treated with MTX is low. Hepatotoxicity incidence is higher in cancer patients who are treated with higher MTX dose.[8]

The median MTX duration therapy in group with liver dysfunction is 43 weeks and without liver dysfunction is 44 weeks. In this study, there is no significant association between MTX duration therapy and liver dysfunction. This result could be caused by short MTX duration therapy. Sotoudenamesh et al studies found significant association between MTX duration therapy and liver dysfunction. In Sotoudenamesh et al study, MTX duration therapy in group with liver dysfunction reached 59.6±42.3 months.[10]

MTX duration therapy is associated with MTX cumulative dose. However, hepatotoxicity is more associated with time interval between two drug administrations than the MTX duration therapy. In study by Rau et al, hepatotoxicity is not a significant side effect in weekly low dose MTX therapy. Patients are more tolerant with weekly MTX therapy than daily MTX therapy.

Conclusion

Based on this study, it could be concluded proportion of RA patients who have liver dysfunction caused by MTX therapy in RSCM is 42.70%. Gender, age, MTX cumulative dose, and MTX duration therapy do not have any statistically significant association with liver dysfunction.

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Clinical Manifestation and Laboratory Finding of Sclerosis Systemic Patient in Dr. Hasan Sadikin General Hospital Bandung : A Descriptive Quantitative Study

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Abstract

Background Systemic sclerosis is a chronic progressive multisystem autoimmune disease in connective tissue, characterized by its heterogeneous clinical manifestation. The purpose of this study is to give information regarding clinical manifestations and laboratory findings of systemic sclerosis patients to establish diagnosis of disease.

Methods This study was conducted using descriptive quantitative design in September—October 2016. Data was collected from medical records of patients visiting Rheumatology Clinic Dr. Hasan Sadikin General Hospital from 1 July 2015—30 June 2016 using total sampling method. The collected data were expected to comprise patient's clinical manifestation and laboratory finding.

Results Most of patients had cutaneous 57 (100.0%) and musculoskeletal 40 (70.2%) involvement. Some of the disease manifestations were Raynaud's phenomenon 38 (66.7%), fingertip lesion 33 (57.9%), stiffness in skin 34 (59.6%), and arthalgia 29 (50.9%). Gastrointestinal involvements were present in 29 (50.9%) patients. Renal involvement were determined from urinalysis result showed proteinuria 10 (17.5%) and hematuria 8 (14.0%), found in 24 (42.1%) patients, while pulmonary and cardiac involvements were found in 30 (52.6%) patients, acknowledged from clinical symptoms such as dyspnea 12 (21.1%). Identification of autoantibodies was found in 12 (21.1%) patients, with 10 (17.5%) patients had reactive ANA and 3 (3.5%) had positive anti-Scl70.

Conclusion Most of systemic sclerosis patients had cutaneous involvement. Renal, pulmonary, and cardiac involvement were concluded based on laboratory findings.

Keywords:
Systemic sclerosis, clinical manifestation, laboratory finding

Introduction

Systemic sclerosis (SSc) is a chronic progressive multisystem autoimmune disease in connective tissue, characterized by its heterogeneous clinical manifestation. Pathophysiologic processes that occur on this disease are vascular abnormality, fibrosis due to collagen deposits and excessive extracellular matrix and autoimmunity.[1] Based on cutaneous involvement patterns, clinical manifestations and laboratory findings, systemic sclerosis is classified into 2 types: diffuse and limited systemic sclerosis. Cutaneous involvement in diffuse systemic sclerosis extend up to proximal knees and elbows, face and trunk. Raynaud's phenomenon usually follows cutaneous manifestations. Organ involvement such as musculoskeletal, kidneys, heart and lungs often appear. Signs of limited systemic sclerosis are known from the mnemonic CREST syndrome, consisting of calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia.[2]

Ten years survival rate of systemic sclerosis patient has increased significantly from 53% in 1970s to 67% in 1990s.[3] However, this rate is lower than SLE patients, which is 93%.[4] A previous study stated that most frequent cause of death in systemic sclerosis patients is related to heart and lungs involvement.[5] Irreversible organ involvement following disease progression may further complicates the disease, hence the long-term prognosis of systemic sclerosis depends on organ involvement and disease manifestation.

Systemic sclerosis is the third most common patients in rheumatology clinic Dr. Hasan Sadikin General Hospital, after systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[6] Most of them often delayed referral, diagnosis, and management of systemic sclerosis from primary health care and district hospital take place. As a consequences, patients come to rheumatology clinic Dr. Hasan Sadikin General Hospital Bandung in severe condition with multiple organ involvement. Delayed referral corresponds with the low education profile of health care provider regarding clinical manifestation and laboratory findings of systemic sclerosis. As a result, a study about clinical manifestations and laboratory findings of systemic sclerosis patient is needed as an important information to help health care providers establish early diagnosis as a way to prevent irreversible organ involvement.

Methods

This study conducted during September–October 2016 at rheumatology clinic Dr. Hasan Sadikin General Hospital Bandung. Medical records of patients was analyzed and presented descriptively using a retrospective method. Sample was selected using total sampling method. Subjects of this study were patients diagnosed with systemic sclerosis who were treated at rheumatology clinic Dr. Hasan Sadikin General Hospital Bandung during July 1, 2015 to June 20, 2016. After ethical clearance letter had been issued, clinical manifestations and results of supportive examination that the patient took were recorded from their medical records. Afterwards, data were grouped based on cutaneous, gastrointestinal, renal, cardiac and pulmonary involvement. The exclusion criteria of the study was patients who have not been completed data on their medical records and patients with overlap syndrome or mixed connective tissue disease (MCTD).

Results

Total participants who fulfilled inclusion were 57 patients. Table 1 showed characteristic of systemic sclerosis patients in rheumatology clinic Dr. Hasan Sadikin General Hospital. The table showed that most of systemic sclerosis patients was female 56 (98.2%) with age range from 31–40 years 19 (33,3%).

Table 1. Characteristics of SSc patients at rheumatology clinic Dr. Hasan Sadikin Bandung General Hospital in July 2015–June 2016

Characteristics	Frequency (n=57)	Percentage (%)
Sex		
Female	56	98.2%
Male	1	1.8%
Age		
<20 years	1	1.8%
20-30 years	9	15.8%
31-40 years	19	33.3%
41-50 years	17	29.8%
51-60 years	5	8.8%
>60 years	6	10.5%

Table 2 showed the distribution of clinical manifestation in involved organ on patients with systemic sclerosis at rheumatology clinic Dr. Hasan Sadikin General Hospital Bandung. The table showed that all 57 subjects are patient with cutaneous involvement (100.0%). Raynaud's phenomenon was found in 38 (67.9%) patients.

Table 2. Distribution of clinical manifestations on organs involved in SSc patients at rheumatology clinic Dr. Hasan Sadikin General Hospital Bandung in July 2015–June 2016

Clinical Manifestation	Frequency (n=57)	Percentage (%)
Skin	n = 57	100.0%
Raynaud's Phenomenon	38	66.7%
Fingertip lesion	33	57.9%
Telangiectasia	9	15.8%
Calsinosis cutis	21	36.8%
Sclerodactyly	25	43.9%
Hardened skin	25	43.9%
Skin stiffness	34	59.6%
Painful skin	26	45.6%
Itchy skin	16	28.1%
Mask-face	8	14.0%
Fish mouth	22	38.6%
Salt and pepper appearance	19	33.3%
Gastrointestinal	n = 29	50.9%
Nausea	14	24.6%
Difficulty in swallowing	13	22.8%
Epigastric pain	6	10.5%
Diarrhea	4	7.0%
Musculoskeletal	n = 40	70.2%
Swelling fingers	14	24.6%
Arthalgia	29	50.9%
Myalgia	13	22.8%
Joint stiffness	10	17.5%
Muscle contracture	2	3.5%
Knee pain	6	10.5%
Back pain	4	7.0%
Renal	n=24	42.1%
Pulmonary and cardiac	n=30	52.6%

Table 3 showed multiple of organ involvements in systemic sclerosis patient. Most patients (40.4%) had combination of skin, musculoskeletal, and gastrointestinal organ

Table 3. Distribution of multiple organ involvements in SSc patients at rheumatology clinic Dr. Hasan Sadikin General Hospital Bandung in July 2015–June 2016

Multiple Organ Involvements	Frequency (n=57)	Percentage (%)
Skin only	13	22.8%
Skin and musculoskeletal	16	28.1%
Skin and gastrointestinal	5	8.8%
Skin, musculoskeletal, and gastrointestinal	23	40.4%

Table 4 showed the distribution of constitutional symptoms which appeared on systemic sclerosis patients at rheumatology clinic Dr. Hasan Sadikin General Hospital. The table showed that the most frequent constitutional symptoms experienced by patients were easy fatigability 12 (21.1%) and weakness 11 (19.3%).

Table 4. Distribution of constitutional symptoms in SSc patients at rheumatology clinic Dr. Hasan Sadikin General Hospital Bandung in July 2015–June 2016

Constitutional Symptom	Frequency (n=57)	Percentage (%)
Easily fatigue	12	21.1%
Weakness	11	19.3%
Hair fall	6	10.5%
Epistaxis	4	7.0%
Weight loss	8	14.0%

Renal, cardiac and pulmonary involvement in patients with systemic sclerosis can be assessed from clinical manifestations and/or supporting examination. Examinations which usually carried out were routine urinalysis, serum creatinine, plain

chest x-ray, chest CT scan, spirometry and echocardiography. Table 5 showed the distribution of clinical manifestations and laboratory findings of systemic sclerosis patients with renal, cardiac and pulmonary involvement at Dr. Hasan Sadikin General Hospital.

Tabel 5. Distribution of clinical manifestations and laboratory findings on renal, cardiac, and pulmonary involvement in SSc patients at rheumatology clinic Dr. Hasan Sadikin General Hospital Bandung in July 2015−June 2016

Organ Involvement	Frequency (n=57)	Percentage (%)
Renal Involvement	n=24	42.1%
Clinical manifestation		
Dysuria	6	10,5%
Oligouria	2	3,5%
Laboratory findings		
Urinalysis		
Proteinuria	10	17,5%
Hematuria	8	14,0%
Bakteriuria	3	5,3%
Increased creatinine serum	4	7,0%
Pulmonary and Cardiac Involvement	n=30	52,6%
Clinical manifestation		
Dyspnea	12	21,1%
Dyspnea with edema in lower	2	3,5%
extremities	7	12,3%
Dyspnea with cough	5	8,8%
Cough	2	3,5%
Palpitation		
Laboratory findings		
Plain chest x-ray	2	3,5%
Cardiomegaly	5	8,8%
Cardiomegaly without pulmonary	2	3,5%
edema	1	1,8%
Suspected ILD		
Idiopathic pulmonary fibrosis	3	5,3%
CT Scan		
ILD appearance	2	3,5%
Spirometry	4	7,0%
Mild restrictive		
Moderate restrictive	2	3,5%
Echocardiography	1	1,8%
Pulmonary hypertension		
Diastolic dysfunction		

Table 6 showed the distribution of autoantibody test result on systemic sclerosis patients at Dr. Hasan Sadikin General Hospital Bandung. The tests included antinuclear antibody (ANA) and anti-Scl70.

Table 6. Distribution of autoantibody test in SSc patients at rheumatology clinic Dr. Hasan Sadikin General Hospital Bandung in July 2015−June 2016

Autoantibody	Frequency (n=57)	Percentage (%)
Autoantibody test	n=12	21.1%
ANA		
Reactive	10	17.5%
Speckled pattern	2	3.5%
Nuclear pattern	3	5.3%
Homogenous type	3	5.3%
Not-specified	2	3.5%
Non-reactive	2	3.5%
Anti-Scl70		
Positive	3	5.3%
N/A	45	78.9%

Discussions

It was obtained from this study that most patients with systemic sclerosis were female 56 (98.2%) with age range from 31-40 years 19 (33.3%). This result corresponded with previous study conducted by Pagalavan dan Ong in Malaysia, where most systemic sclerosis patients were 31−40 years old female.[7]

All systemic sclerosis patients showed cutaneous involvement as disease manifestation. This result suited to previous study which stated that even though clinical manifestations in systemic sclerosis were heterogeneous, most patients had cutaneous involvement.[8] Systemic sclerosis patients which showed clinical manifestation and positive laboratory findings on organs without any cutaneous involvement were called systemic sclerosis sine scleroderma (ssSSc). On a study conducted by Marangoni, et al., in Brazil, it was found that among 947 systemic sclerosis patients, there were only 79 (8.3%) patients with ssSSc.[9]

Based on Le Roy vascular hypothesis, dysfunctional blood vessel was an initial pathophysiologic process in systemic sclerosis marked by Raynaud's phenomenon.[10] The result of this study revealed that the most frequent clinical manifestation found on skin was Raynaud's phenomenon (66.7%). This result corresponded with a previous study conducted by Pagalavan and Ong in Malaysia, where 38 (83.6%) patients with systemic sclerosis experienced Raynaud's phenomenon.[7] Hanitsch in Germany published a higher rate; 1160 (96.7%) patients experienced Raynaud's phenomenon.[11]

This study revealed that 9 (15.8%) patients experienced telangiectasia and 21 (36.8%) patients experienced cutaneous calcinosis. This result was different with the study by Pagalavan and Ong in Malaysia, where 28 (45.9%) patients experienced telangiectasia and 7 (11.5%) patients experienced calcinosis cutis.[7] The result might be affected by the type of systemic sclerosis experienced by patients, calcinosis cutis was more frequently found in limited systemic sclerosis.[12]

Musculoskeletal involvement as the main cause of disability was frequently found on systemic sclerosis.[13] From the study result, it was revealed that 40 (70.2%) systemic sclerosis patients had a musculoskeletal involvement. The most frequently found manifestation was arthalgia 29 (50.9 %). This result was suitable with the previous literature which stated that the most common clinical manifestation on musculoskeletal involvement was arthalgia.[14] This result corresponded with the study by Pagalavan and Ong in Malaysia which reported that arthalgia/arthritis were frequently found (49.2%).[7]

There were 29 (50.9%) systemic sclerosis patients in this study with gastrointestinal involvement. The most manifestation which frequently found was difficulty in swallowing 13 (22.8%). This result corresponded with previous study which stated that gastroesophageal reflux and dysphagia were the frequent manifestations of systemic sclerosis on patients.[15] The other common complaint were nausea 14 (22.8%). These gastrointestinal manifestations were one factor which might cause malnutrition on systemic sclerosis patients. Baron, et al reported 18% patients were at risk for malnutrition.[16]

On this study, the most frequent constitutional symptoms reported by systemic sclerosis patients were fatigue (21.1%) and weakness (19.3%). This result suited to previous study by Sandusky, et al., in USA which stated that 76% subjects experienced fatigue, while 61% of those patients stated that this was one of the most physically and socially disturbing symptoms.[17]

Renal involvement on systemic sclerosis patients can be assessed from clinical features or from supporting examination. On this study, there were 24 (42.1%) patients with renal involvement; 8 (14.0%) patients with clinical symptoms such as dysuria (10.5%) and oliguria (3.5%), while the rest of them had abnormal supporting examination test result. The supporting examinations conducted were routine urinalysis and serum creatinine level. Abnormalities found on patients from those test were proteinuria (17.5%), hematuria (14.0%) and bacteriuria (5.3%). Albuminuria could be used as vasculopathy marker, which was one of the pathophysiologic processes on systemic sclerosis.[18] On this study, increasing creatinine serum level was found on 4 (7.0%) patients. The increasing creatinine serum level did not completely describe a renal dysfunction, since renal dysfunction could also occur on patients with normal creatinine serum level.[18]

There were 30 (52.6%) patients on this study showed cardiac and pulmonary involvement marked by clinical manifestations and supporting examination. On this study, there were 12 (21.1%) patients with dyspnea, 2 (3.5%) patients with dyspnea and edema on extremities and 7 (12.3%) patients with dyspnea and cough. Meanwhile, a study by Hanitsch in Germany reported 390 (32.5%) patients had dyspnea.[11] Patients with dyspnea needed further observation and screening for pulmonary hypertension. The most frequent pulmonary manifestations and the main cause of death on 60% systemic sclerosis patients were interstitial lung disease (ILD) and pulmonary hypertension.[19] From plain chest x-ray and chest CT scan, respectively there were 2 (3.5%) and 3 (5.3%) patients with interstitial lung disease, while from echocardiography there were 2 (3.5%) patients with pulmonary hypertension. Systolic and diastolic dysfunction are early signs of heart problems on patients with systemic sclerosis.[20] On this study, there were 1 (1.8%) patients presented with diastolic dysfunction from echocardiography.

One of the pathophysiologic process occur on systemic sclerosis is the synthesis of autoantibody. The number and level of this autoantibody fluctuates depending on the disease activity, hence it could be used as diagnostic markers and determine prognosis of systemic sclerosis.[2] There were 10 (17.5%) patients on this study had positive ANA (antinuclear antibody) test result while 3 (5.3%) patients with positive anti-Scl70. This result was different from Pagalavan and Ong in Malaysia who stated that there were 51 (83.6%) patients with positive ANA and 21 (34.4%) patients with positive anti-Scl70 test result. This difference because not all patients who were treated at rheumatology clinic Dr. Hasan Sadikin General Hospital had autoantibody tests.[7]

Conclusion

From 57 sample, it could be concluded that most systemic sclerosis patients had cutaneous involvement, renal, pulmonary, and cardiac involvement based on laboratory findings.

This study was a retrospective study that evaluated history taking and supporting examination test result on medical records. Most of the medical records had not been on computerized system, hence there could still be a possibility that there were mistakes in interpreting the writings on the medical records. On the other hand, not all patients took autoantibody test hence their records were not reported.

Recommendation from this study is demographic data on medical records could be completed. The medical records should also comprise the recordings of all examination the patient took to help clinician establish the diagnosis of the patient.

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Correlation of sCD40L Level with Force Vital Capacity Value in Restrictive Lung Disease of Systemic Sclerosis Patients

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Abstract

Background: Interstitial Lung Disease (ILD) is one of the major cause of morbidity and mortality in Systemic Sclerosis (SSc). The gold standard to diagnose ILD is using High Resolution Computed Tomography (HRCT) scan. HRCT scan need a lot of cost and not always available, so another diagnosing test is needed as an alternative modality to diagnose ILD. ILD is a restrictive lung disease caused by lung fibrosis which is proved by the decrease of Forced Vital Capacity (FVC) in spirometry, and followed by the increase of soluble CD40L (sCD40L) level in plasma. This sCD40L may become a potential biomarker to evaluate lung fibrosis in SSc patients. The aim of this study is to analyze the correlation of sCD40L levels with FVC score in SSc patients with restrictive lung disease.

Method: This cross sectional study was enrolled by the SSc patient who has restrictive lung disease based on spirometry test, at Rheumatology outpatient clinic dr. Hasan Sadikin Hospital from May 2015 to May 2016. All subject took underwent history, physical examination, spirometry and blood test for sCD40L. Data were analyzed using Pearson correlation.

Result: There were 38 subjects involved in this study, dominated bywoman (92.1%) with mean age 41(±11) years. Subjects consist of 22(57,9%) with limited SSc, 16(42,1%) with diffuse SSc patients and 33 subjects treated with DMARD. Mean sCD40L serum in this study was 6.690,3(±2.377,3) pg/mL, with no statistical difference between limited and diffuse type (p=0.154). Mean FVC score in this study was 58.2(±10,8). There was no significant correlation between sCD40L serum with FVC (r=0.058; p=0.366). There was weak correlation on DMARD naïve subject between sCD40L serum and FVC (r=0.058; p=0.366) but statistically insignificant. There was no significant correlation between sCD40L serum with mRSS (r=0,066; p=0,346).

Conclusion: This study founds no correlation between sCD40L with FVC in SSc at dr. Hasan Sadikin Hospital.

Keyword: sCD40L, Forced Vital Capacity, Restrictive Lung Disease, Systemic Sclerosis

Introduction

Systemic Sclerosis (SSc) is a chronic progressive autoimmune connective tissue disease that involving many organs. The etiology of this disease is still not well known.[1-3] Lung is common organ involved in systemic sclerosis patients, such as Interstitial Lung Disease (ILD) and pulmonary arterial hypertension.[4] Systemic Sclerosis patients suffered with ILD tend to has lower quality of life compared to healthy person.[5] European Scleroderma Trials and Research (EUSTAR) group reported ILD was a major cause of death in systemic sclerosis. Data of 5800 systemic sclerosis patients showed as much as 35% deaths caused by pulmonary fibrosis, 26% by pulmonary arterial hypertension and 4% by kidney disorder.[6]

ILD is difficult to diagnose, especially in developing country, due to unavailability of High Resolution Computed Tomography (HRCT) scanning which is the gold standard for diagnosing ILD.[4,7,8] Moreover, it is not affordable for the most patients. Other pulmonary function tests are more commonly used as initial screening of ILD in systemic sclerosis patients in our center.[4,7] Those PFT instruments consist of test for diffusing capacity of the lung for carbon monoxide (DL_{CO}), spirometry to define forced vital capacity (FVC), etc. The pulmonary function tests (PFT) play as key role to determine the severity of pulmonary complication in SSc patients. FVC is one of the common test which use to determine the severity of restrictive abnormality in ILD.[8]

T-cells trigger fibroblasts activation which causing fibrosis process in systemic sclerosis patients. Activated CD4 T-cells will express CD40 ligand (CD40L/CD154) that binds to CD40 on the surface of the B-cells. T cells will produce cytokines and stimulate fibroblast to start fibrosis cascade as the main pathogenesis of systemic sclerosis.[9] CD40L is suggested playing role in fibrosis cascade. CD40L can be cleaved from the cell surface, releasing a soluble CD40L (sCD40L) which is biologically active.[10,11] Allanore, et al reported an increase of plasma sCDL40 associated with vascular complication in systemic sclerosis patients. Instead, other studies reported controversially role of CD40-CD40L bond in pulmonary fibrosis.[11,12]

Aim of this study is to analyze the correlation of sCD40L level with FVC value in restrictive lung

disease of systemic sclerosis patients.

Method

This cohort retrospective study enrolled the systemic sclerosis patients who had restrictive lung disease based on spirometry test. Data were collected from outpatient subjects at clinic rheumatology, Hasan Sadikin General Hospital from May 2015 to May 2016. The inclusion criteria were patients who diagnosed with systemic sclerosis based on ACR/EULAR 2013 criteria with restrictive lung disorders and willing to participate in this study, includes carried out blood test and spirometry examination. Exclusion criteria were patients who diagnosed with other autoimmune diseases and/or diagnosed with restrictive lung disease other than ILD through history, physical examination and history from previous medical records.

This study used two step of data collection. Initial step was screening to get subjects who meet the inclusion and exclusion criteria. The next step was venous blood sampling to determine the sCD40L level followed by spirometri test to evaluate FVC value. Then data was analyzed with Pearson correlation test.

Result

We included 38 patients in this study. Characteristics of the subject are shown at table 1.

Table 1. Characteristics of Subjects

Characteristics	All Subjects n=38	Limited Type n=22 (57.9%)	Diffuse Type n=16 (42.1%)
Age (mean ± SD) years	41 ± 11		
Sex			
Male (n%)	3 (7.9)		
Female (n%)	35 (92.1)		
Treatment History			
Methotrexate (n%)	33 (86.8)		
Steroid (n%)	33 (86.8)		
Cyclophosphamide (n%)	2 (5.3)		
DMARD-naïve (n%)	5 (13.2)		
mRSS (median, range)	17 (4 – 36)	12 (4 – 23)	27 (10 – 36)
FVC (mean ± SD)	58.2 ± 10.8	57,1 ± 12,7	59,6 ± 7,5
sCD40L (mean ± SD) (pg/mL)	6690.3±2377.3	6218,0 ± 2170,7	7339,8 ± 2562,5

The median of modified Rodnan Skin Score (mRSS) is 17 and has range 4 to 36. Mean of FVC by spirometry examination was 58.2 ± 10.8. The most were 15 (40%) moderate restrictive lung patients, 10 (26%) severe restrictive lung patients, 8 (21%) moderate to severe restrictive lung patients, and 5 (13%) mild restrictive lung patients. Mean of sCD40L was 6690.3±2377.3 pg/mL. There were no statistically different of sCD40L level and FVC value between diffuse type and limited type systemic sclerosis subjects.

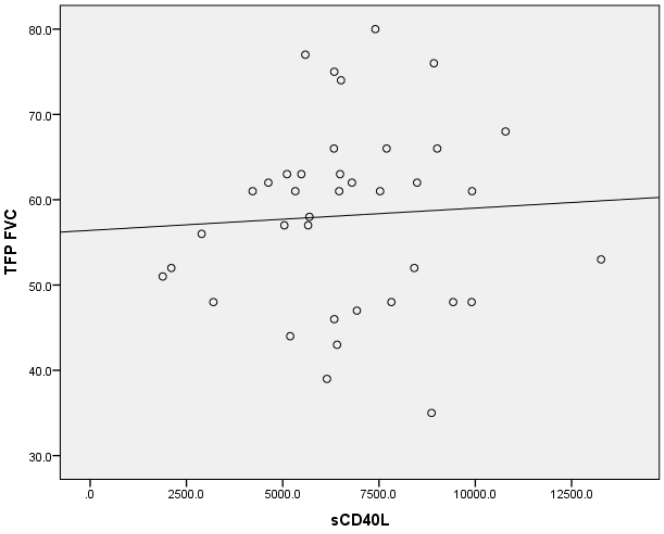
There was five (13.2%) subjects who were for the first time diagnosed as systemic sclerosis and had never taken DMARD treatment before this study. mRSS score was higher in DMARD-naïve patients (p = 0.036, Mann-Whitney) sCD40L and FVC had no different between DMARD patients and DMARD-naïve patients shown in table 2.

Tabel 2. Difference between DMARD and DMARD-naïve patients

Variabel	DMARD-naïve n=5	DMARD n=33	*p-value*
mRSS *(median, range)*	32 (15 – 36)	14 (4 – 34)	**0.036**
sCD40L *(mean ± SD)*	5909.8 ± 783.8	6808.6 ± 2519.5	0.438
FVC *(mean ± SD)*	58.4 ± 9.1	58.1 ± 11.1	0.958

Bivariate test was used to analyze correlation between sCD40L level and FVC value revealed that sCD40L was not correlated with FVC (r=0.058, R^2 = 0.0034, p=0.366, Pearson correlation). Figure 1 show scatter diagram of this study.

Figure 1. Scatter diagram between sCD40L and FVC



There was weak correlation on DMARD naïve subject between sCD40L serum and FVC (r=-0.225; p=0.358, Pearson correlation) but not significant as shown in table 3.

Tabel 4. Bivariate Analysis between sCD40L and FVC in DMARD and DMARD-naïve Patients

Variable	Patients	FVC	
		r	*p-value*
sCD40L	DMARD-naïve	-0.225	0.358
	DMARD	0.069	0.351

Discussion

Average age of the subjects was 41±11 years, it is in accordance with the onset of systemic sclerosis disease which the highest in the fourth and fifth decade.[13,14] Mean age was smaller compared to the research conducted by Allanore et al (50 subjects) 57±11 years and Komura et al (49 subjects) 51.4±15.6 years but in accordance with study on Asian population in Singapore by Low et al (200 subjects), namely 46±14.9 years.[11,15,16] This difference maybe due to race differences in both populations. So, age of systemic sclerosis patient in Caucasian population is older than in Asian populations.

Most of the subjects were women (92.1%). These results were differed by the proportion of women and men incidence in US that reached 3−5:1.[1,14,17] But, similar to the result obtained by Komura, et al. study in Asia (92%) and Low research in Singapore (86%).[15,16]

Mean FVC value by spirometry was 58.2±10.8%. All subject as restrictive lung disorder that may be a pulmonary fibrosis. There was no difference in FVC value between limited type and diffuse type subjects (p=0.482). Abnormalities of pulmonary fibrosis is more common in diffuse type since it is a rapidly progressing disorder that affects a large area of the skin and compromises one or more internal organs including lung. Expression of antinuclear antibody is more dominant in diffuse type SSc compared to the limited type.[1] FVC examination can be used as an initial screening test but the incidence of pulmonary fibrosis may not be used as the gold standard to diagnosis pulmonary fibrosis.

Mean of sCD40L levels in our study were 6690.3±2377.3 pg/mL. This is higher when compared with control values in Allanore, et al study (median sCD40L 79 (50−118) pg/mL) and Salibi, et al. study (mean sCD40L 717 pg/mL). sCD40L levels in our study is also higher than sCD40L level in systemic sclerosis patients in Allanore, et al. study with a median sCD40L 495 (10−2690) pg/mL and Salibi, et al study with a mean sCD40L 1564 pg/mL.[11,18] This difference happened due to the difference subjects involved in Allanore, et al study used all systemic sclerosis patients with or without pulmonary complication, while in the Salibi, et al study, the subjects were included the lung fibrosis subjects with any underlying disease. Whereas the subjects in our study were the systemic sclerosis patients with restrictive lung disorders. CD40L is believed to play role in the fibrosis cascade of systemic sclerosis patients. CD40-CD40L bond between T-cells and B-cells trigger proliferation and differentiation of B-cells into plasma cells and forms a bond autoantibody.[19,20] CD40-CD40L activates the proliferation of fibroblasts, produces pro-inflammatory cytokines, and begins fibrosis process.[21,22] Komura and Fukasawa reported the increase of plasma CD40 protein due to CD40 expression on fibroblasts surface in systemic sclerosis patients.[15,21] CD40L can be cleaved from cell surface and dissolved as a soluble CD40L on plasma that biologically active.[10,23]

From our study, we found no statistically correlation between sCD40L level and FVC (r=0.058, R^2=0.0034, p=0.366). This is consistent with Allanore, et al study that reported lack correlation between sCD40L levels with pulmonary fibrosis and carbon monoxide diffusing capacity (DL_{CO}).[11] Other study by Salibi, et al reported a significantly increasing of sCD40L levels in pulmonary fibrosis patients when compared to the healthy population ($p < 0.05$).[18] Salibi, et al also reported a correlation sCD40L level with FVC (R2=0.16, r=0.4) but not significantly related (p=0.16).[12]

There are some differences between our study and the study conducted by Allanore, et al or Salibi, et al. This study included 38 subjects while Allanore, et al study followed by 50 subjects and Salibi et al study followed by 13 subjects. This study uses retrospective cohort while the two other studies using cross sectional method. This research together with Salibi, et al analyzed the correlation of sCD40L levels with the value of FVC, while Allanore, et al analyzed the association of sCD40L levels with the incidence of pulmonary fibrosis and DL_{CO}.

Other difference is our study and Allanore, et al study used systemic sclerosis patients, while Salibi, et al. research used all subjects with pulmonary fibrosis. Study conducted by Allanore, et al only involve systemic sclerosis patients who have not received immunosuppressive therapy, while in our study, only five subjects who have not received immunosuppressive therapy and the remaining subjects have been treated with methotrexate.

Different level of sCD40L may be affected by several conditions in our subject settings. First, 83.8% subject has been treated with DMARD (methotrexate, cyclophosphamide). Methotrexate could interfere activation of T-cell that might affect the level of sCD40L.[24] Second, we measured sCD40L to represent the activity of CD40L, because sCD40L has the CD40L biologic activity. However, there were not any data about the equivalent of sCD40L level on serum and CD40L level on T-cell. Third, many factors could interfere the result of FVC measurement such as age, sex, weight, height, chest abnormality. Fourth, disease activity shown by sCD40L level might fluctuate rapidly while lung damage shown by FVC level might be change in a slow progression.

Conclusion

Our study showed increased plasma soluble CD40 ligand concentrations in restrictive lung disease of systemic sclerosis patients. Our result found no significant correlation between sCD40L with FVC in SSc at dr. Hasan Sadikin General Hospital.

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Validation of Modified COPCORD Questionnaire Indonesian Version as Screening Tool for Joint Pain and Musculoskeletal Diseases

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Abstract

Background: WHO-ILAR COPCORD Program is a program that aimed to obtain data on joints pain and musculoskeletal diseases in developing countries, one aspect which has not been studied is the ability of COPCORD questionnaire as a screening tool which standardized for screening joint pain and musculoskeletal diseases. Objective of this study is to assess the validity of modified COPCORD questionnaire Indonesian version in screening joint pain and musculoskeletal disease compared to examination by rheumatologists.

Methods: The initial phase of the research is determining essential points, translation to Indonesian, and back translation. The second stage is testing questionnaires in communities which 100 respondents involved. Dependent variable is the diagnosis of rheumatic diseases and independent variables are pain in less and more than 7 days, high degree pain in less and more than 7 days, history of NSAIDs/Steroids/DMARDs use, and disabilities. Validation test was assessed by calculating the sensitivity, specificity, PPV, NPV, LR+, and ROC curve. Bivariate analysis using Chi Square analysis, and multivariate analysis using logistic regression.

Results: The sensitivity test results is best obtained on the question history of NSAIDs/steroids/DMARDs use (100%) and specificity is best obtained on the question about disability (98%). ROC curve analysis which the results >85% obtained on the question of pain >7 days (90%), high degree pain >7 days (93%), and history of NSAIDs/steroids/DMARDs use (92%). LR+ to diagnose rheumatic diseases found in all questions. Chi square analysis showed that all questions were significant with $p < 0.05$ and odds ratio (OR) obtained most on high degree pain more than 7 days (OR: 180.167; 95% CI: 38.196-849.834).

Conclusion: The modified COPCORD questionnaire Indonesian version has been adapted and can be a good tool in the screening of joint pain and musculoskeletal diseases compared to examination by rheumatologists.

Keyword: Validation, Questionnaire, COPCORD

Introduction

Joint pain and musculoskeletal disease is the most common cause of morbidity in general population. Even rheumatic diseases not increase mortality but it can lead to disabilities and low quality of life and productivity.[1] On the other hand the need of data on the magnitude of the problem and the effects of joint and musculoskeletal diseases is very important, especially in developing countries such as Indonesia. Based on these data we can see the effect of the disease and provide recommendation and intervention plan both in terms of detection and therapy.[2]

In the 1981 the International League against Rheumatism (ILAR) and the World Health Organization (WHO) jointly launched the WHO-ILAR Community Oriented Program for the Control of Rheumatic Diseases (COPCORD) to obtain data on the joints and musculoskeletal diseases in developing countries. COPCORD is a low cost program which requires minimal infrastructure by relying on existing resources. Using the same and validated method, COPCORD Phase 1 (out of 3 phase) has been succeeded to collect data from Australia,[3] Bangladesh,[4] Brazil,[5] Chile,[5] China,[6] Cuba,[7] Egypt,[8] Guatemala,[9] India,[10] Indonesia,[11] Iran,[12] Kuwait,[13] Malaysia,[14] Mexico,[5, 15] Pakistan,[16] Philippines,[17] Thailand,[18] Taiwan,[19] Tunisia[20] and Vietnam.[10, 21-23]

One aspect of COPCORD which has not been studied is the ability COPCORD questionnaire as a screening tool that is standardized in rheumatic diseases. For population who has limited health facility level or limited time and resources, this questionnaire would be more suited to be applied in a broad population. The consideration of COPCORD as a standardized tool, requires validation of certain aspects like diagnostic tests, especially when compared to complete examination conducted by rheumatologist.[24, 25] In the other hand, the adaptation and translation into Indonesian questionnaire also have consequences in language and cultural adaptation that may be different from the original.[26] Based on this fact, it is necessary to validate a modified COPCORD questionnaire Indonesian version for screening of joint pain and musculoskeletal diseases in Malang.

The aim of this study is to assess the validity of modified COPCORD questionnaire Indonesian version, for screening joint pain and musculoskeletal disease in the population compare to examination done by rheumatologist.