RESEARCH ARTICLE

A Double-Blind, Randomized Controlled Trial of Hydroxychloroquine for Cognitive Dysfunction and Inflammatory Biomarkers in Systemic Lupus Erythematosus Patients in Indonesia

Bantar Suntoko[1,*], Suharyo Hadisaputro[2], Handono Kalim[3], Suyanto Hadi[4], Ika Vemilia Warlisti[4]

[1]Doctoral Program of Medical and Health Science, Faculty of Medicine, Universitas Diponegoro, Jl. Dr. Sutomo No.16, Semarang 50244, Indonesia
[2]Division of Tropical Infectious Diseases, Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro/Dr. Kariadi General Hospital, Jl. Dr. Sutomo No.16, Semarang 50244, Indonesia
[3]Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya/Dr. Saiful Anwar Hospital, Jl. Jaksa Agung Suprapto No.2, Malang 65112, Indonesia
[4]Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro/Dr. Kariadi General Hospital, Jl. Dr. Sutomo No.16, Semarang 50244, Indonesia

*Corresponding author. Email: bantar28@gmail.com

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Abstract

BACKGROUND: Systemic lupus erythematosus (SLE) is an autoimmune condition characterized by persistent, chronic inflammation that damages organ tissue. One of the symptoms that is often found in SLE is cognitive dysfunction. Hydroxychloroquine is recommended for the treatment of all levels of SLE. This study was conducted to prove the influence of hydroxychloroquine on improving cognitive function and inflammatory biomarkers compared to standard therapy.

METHODS: The study adopted randomized controlled trial (RCT) in SLE patients with cognitive dysfunction who met the inclusion criteria. The treatment group consisted of 26 subjects who received hydroxychloroquine 200 mg/day for 8 weeks and standard therapy, while the control group consisted of 29 subjects who were given standard therapy only. Examination of Montreal Cognitive Assessment (MoCA)-INA, interleukin (IL)-6, IL-4, interferon (IFN)-α, and C-reactive protein (CRP) scores was carried out at the beginning and the end of the study. The unpaired variables were examined with independent T-test or the Mann-Whitney test, while the paired variables were examined with paired T-test or Wilcoxon signed rank test. The Spearman correlation test was used to measure correlation between variables.

RESULTS: A total of 55 subjects participated and completed the study. The result showed a significant relationship between hydroxychloroquine and decreasing levels of IL-6 and IL-4 ($p<0.05$). Meanwhile, there was no significant effect on the increase in cognitive function and decrease in IFN-α and CRP ($p>0.05$) in both groups.

CONCLUSION: Hydroxychloroquine decreases the levels of IL-6 and IL-4, but has no effect on cognitive function, levels of IFN-α and CRP.

KEYWORDS: hydroxychloroquine, systemic lupus erythematosus, cognitive dysfunction, inflammation

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Introduction

Systemic lupus erythematosus (SLE) is one of the most ordinary types of autoimmune diseases characterized by chronic and persistent inflammation that causes damage to various organ systems.(1,2) Neuropsychiatric SLE (NPSLE) is a clinical syndrome that affects central and peripheral nervous systems, both diffuse and focal. One of the most common abnormalities in NPSLE is cognitive dysfunction, which significantly reduces the quality of life, as well as increases morbidity and mortality. In cognitive dysfunction,

one or more of the following disorders are found, namely memory (learning and recalling), simplex or complex attention, executive ability, visual-spatial processing, language skills, problem-solving, as well as psychomotor speed disorders.(3)

The pathogenesis of cognitive dysfunction is very complex, including the involvement of antigen-antibody complexes, inflammation through the production of cytokines (4), and ischemia that causes nervous system injury (5). The examination of biomarkers pertaining to inflammatory processes in the brain holds significance in understanding the pathophysiology of NPSLE. Some pro-inflammatory cytokines that play a role in the pathogenesis of NPSLE are interleukin (IL)-6, IL-4, interferon-α (IFN-α), and C-reactive protein (CRP).(6) However, the most relevant cytokine in the development of NPSLE is still unclear.

Hydroxychloroquine is recommended for all levels of SLE, from mild to severe, including NPSLE, with a dose not exceeding 5 mg/kg body weight (BW).(7) Studies on the advantages of hydroxychloroquine in SLE patients for improving cognitive function and decreasing inflammatory biomarkers are limited. Hydroxychloroquine has been reported to demonstrate anti-inflammatory properties, which have the potential to affect inflammatory biomarkers within the brain. It is anticipated that the administration of hydroxychloroquine can improve cognitive function in SLE.(8) Consequently, this study was conducted to prove the effect of hydroxychloroquine in improving cognitive function and inflammatory biomarkers compared to standard therapy in SLE patients with cognitive dysfunction. This study used 200 mg/day of hydroxychloroquine according to the 2019 SLE management guidelines by the Indonesian Rheumatology Association (IRA).(9) Hydroxychloroquine is given for eight weeks because the distribution of the drug to cell components to give a therapeutic effect takes 1,300 hours or almost eight weeks.(10)

Methods

This study was categorized as a randomized, double-blind, placebo-controlled trial including subjects recruited consecutively from July 2021 to March 2022. This study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Diponegoro/Dr. Kariadi General Hospital (No. 786/EC/KEPK-RSDK/2021). The procedure was carried out based on the principles of the Declaration of Helsinki.

Study Subjects

The subjects consisted of SLE patients who had been diagnosed based on The European League Against Rheumatism/American College of Rheumatology 2019 (EULAR/ACR 2019) criteria at Dr. Kariadi General Hospital and St. Elisabeth Hospital, Semarang, Indonesia and who met the inclusion criteria.(11) The inclusion criteria were women aged ≥18 years suffering from SLE based on SLE classification criteria according to EULAR/ACR 2019, using the anti-nuclear antibody (ANA) titer as the first step in determining the diagnosis and fulfilling a total score of ≥10 points, willing to join in the study by signing informed consent, who had never taken hydroxychloroquine before, as well as fulfilled the criteria for cognitive dysfunction (if the Montreal Cognitive Assessment (MoCA) score <26). Other inclusion criteria were patients who used steroids ≤12 mg/day, had systemic lupus erythematosus disease activity index (SLEDAI) scores ≤10, and received disease modifying antirheumatic drugs (DMARDs) and steroids in a stable state of disease activity. The exclusion criteria were SLE patients with retinal disorders (retinitis), cardiac conduction abnormalities (arrhythmias), diabetes mellitus, impaired liver function, infections, and signs of malignancy. The sample size for each group was 18 with a minimum total of 36 subjects.

Sampe size : $n1 = n2 = \left\{\frac{(1.96 + 0.84)5.3}{-3.7}\right\}^2$

$= \left\{\frac{(Z\alpha + Z\beta)S}{X1 - X2}\right\}^2$

$= 16$ subjects

Drop out correction : $n_{do} = \frac{n}{1 - do}$

$n_{do} = \frac{16}{1 - 0.1}$

$n_{do} = 17.78 \approx 18$

Zα : Z value corresponding level of significance
Zβ : Z value corresponding level of power
S : Standard deviation
X1 – X2 : The difference the investigator wishes to detect
n1,2 : The sample size in each of the groups
n_{do} : The sample size in each of the groups if there are probabilities of drop out
do : drop out (10% → 0.1)

Each group was given standard SLE therapy, including ≤12 mg methylprednisolone and DMARDs (cyclosporin A,

methotrexate, mycophenolic acid, mycophenolate mofetil, or azathioprine). The treatment group was given 200 mg/day of hydroxychloroquine for 8 weeks, whereas the control group was not given hydroxychloroquine.

The intervention in this study was conducted by double blinding, which involved the encapsulation of hydroxychloroquine preparations in capsules with the same characteristics (color and size). These capsules were placed in a sealed envelope that was previously coded, and the new code was unlocked after the completion of analysis. Furthermore, the packaging (capsule) and coding processes were carried out by a third party and the study analysts involved were unaware of the therapy being administered, while the subject also remained uninformed of the drug being taken.

Data Collection

The data collected included age, education levels, duration of SLE, and type and duration of SLE treatment. Subjects were examined for vital signs and assessed for the presence or absence of hypertension, then their body weight and height were calculated to define body mass index (BMI). The Beck depression inventory (BDI) scale was used to determine if subjects had depression. Laboratory tests were carried out to fulfill the inclusion, including post-prandial blood sugar (normal value <140 mg/dL), fasting blood sugar (normal value = 70 to 100 mg/dL), hemoglobin A1c (HbA1c) (normal value <5.7%), total cholesterol (normal value <200 mg/dL), LDL cholesterol (normal value <130 mg/dL), HDL cholesterol (normal value >40 mg/dL), aspartate transaminase (AST) (normal value = 8 to 33 U/L), alanine transaminase (ALT) (normal value = 4 to 36 U/L), while fundoscopy and electrocardiography (ECG) were performed to rule out retinitis and arrhythmias, respectively. The volume of blood collected from each subject was 5 mL. MoCA score, as well as IL-6, IL-4, IFN-α, and CRP levels were measured in each group before and after treatment.

Post-prandial and fasting blood sugar, lipid examination, as well as AST and ALT measurement were performed using Selectra ProS analyzer (ELITech Group, Puteaux, France). Post-prandial and fasting blood sugar were analyzed with the hexokinase method and the results were expressed in mg/dL. Lipid examination was done to determine the total cholesterol, triglycerides (TG), low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol using phosphate complex inhibition (PAP) method and the results were expressed in mg/dL. Aspartate transaminase (AST) and alanine transaminase (ALT) were analyzed with International Federation of Clinical Chemistry (IFCC) without pyridoxal-phosphate method and the results were expressed in U/L. Meanwhile, HbA1c was measured by high-performance liquid chromatography (HPLC) using Standard F200 Analyzer and the results were expressed in % (SD Biosensor, Gyeonggi-do, Republic of Korea).

IL-6, IL-4, and IFN-α levels were analyzed with Human IL-6, IL-4, and IFN-α ELISA Kit (Elabscience, Houston, TX, USA) and expressed as pg/mL. The optical density (OD) of the sample was measured spectrophotometrically at a wavelength of 450±2 nm. The level of CRP in serum was measured using Nanopia CRP Assay kit (Sekisui Medical, Tokyo, Japan) and was reported as mg/dL. The CRP content is determined by measuring the agglutination as the change of absorbance at wavelengths of 570 and 800 nm.

Statistical Analysis

Data analysis was performed using the SPSS 20 for Windows program (IBM, Armonk, NY, USA). The data and clinical characteristics of the subjects were presented in tabular form. Numerical data was checked for normality using the Shapiro-Wilk test. The normally distributed data was presented as mean and standard deviation, while data that was not normally distributed was presented as median (min-max). The categorical data obtained were presented in the form of amounts and percentages. The unpaired variables were examined with independent t-test or the Mann-Whitney test. The paired variables were examined with paired T-test or Wilcoxon signed rank test. The Spearman correlation test was used to measure correlation between variables. Values of $p<0.05$ indicated the statistical significance.

Results

Subject Characteristics

From a total of 103 respondents from the accessible population, 65 SLE patients with cognitive impairment who had MoCA-INA scores <26 were included in this study as subjects, while the other 38 were excluded. Each subject was randomly assigned to the treatment (n=32) or control (n=33) group. During the study, only 55 subjects took participated, while 10 others were excluded. Therefore, 55 subjects participated in this study to completion, which consisted of 26 treatment subjects and 29 control subjects (Figure 1).

The subjects were found to have an average age of 33.00±10.53 years in treatment group and 34.55±8.15 years in control group. The duration of subjects who suffered

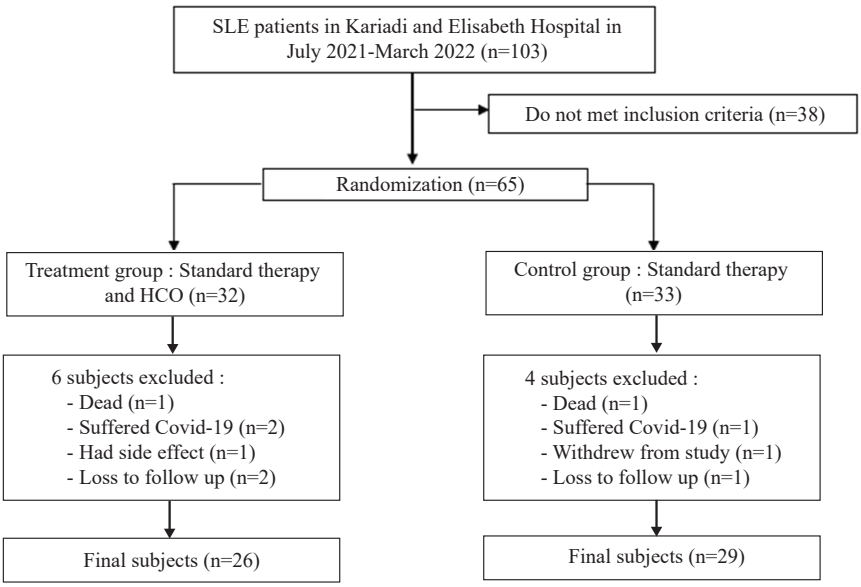

Figure 1. Consolidated Standards of Reporting Trial (CONSORT) flow diagram.

from SLE were 30 (0-138) months in treatment group and 40 (0-163) in control group. The average BMI of subjects in both treatment and control groups were within the normal range. The disease activity in both groups were mild-moderate. In this study, blood pressure, total cholesterol, triglyceride, LDL cholesterol and HDL cholesterol levels in both groups were within the normal range. The BDI was used to assess the respondents' depression levels, and the results showed mild-moderate depression in treatment group and mild depression in control group. Both treatment and control subjects have mild cognitive impairment. Furthermore, the data on subject characteristics showed no significant differences in age, education, duration of SLE, BMI, SLEDAI score, blood pressure, lipid profile, BDI, and MoCA score between subjects in the two groups. This shows successful randomization with minimized bias, as indicated in Table 1.

Response to Hydroxychloroquine Treatment

MoCA score data and cytokine levels in both groups was not normally distributed, as indicated by $p<0.05$ obtained in the normality test. A significant difference was found in delta IL-6 and IL-4 levels ($p<0.05$) between the control and treatment groups. However, there was no significant difference in delta MoCA score as well IFN-α and CRP levels ($p>0.05$) between the control and treatment groups (Table 2). There was a significant correlation between levels of CRP and MoCA score ($p<0.05$), but there was no significant correlation between levels of IL-6, IL-4, as well as IFN-α and MoCA score, and levels of IL-6, IL-4, IFN-α, as well as CRP and sub MoCA score ($p>0.05$) (Table 3, Table 4).

Discussion

This study proved that the administration of hydroxychloroquine could significantly decrease the levels of IL-6 and IL-4. Hydroxychloroquine inhibits the presentation of major histocompatibility complex (MHC) class II to T cells, prevents T cell activation, and reduces the production of IL-6 and IL-4 cytokines by T cells and B cells.(10) The results of previous study showed a decrease IL-6 after administration of hydroxychloroquine, which can be attributed to mRNA reduction due to mRNA imbalance and changes in transcriptional activity. Furthermore, hydroxychloroquine inhibits the synthesis of IL-6 mRNA. (12) It has been demonstrated that the level of nervous system (neurofilament) degradation in NPSLE correlates with IL-6.(13) The mechanism of hydroxychloroquine in reducing IL-4 levels in this study can be explained similarly to the mechanism of inhibition of IL-6. The impact of hydroxychloroquine on IL-4 levels has not yet been investigated in any studies.

The result of this study indicated that the administration of hydroxychloroquine could not reduce IFN-α. This result is contrary to the report of previous study that hydroxychloroquine therapy reduces the level of IFN-α.(14) On the other hand, another study found that hydroxychloroquine has no impact on the production of IFN-α.(15) Since hydroxychloroquine acts slowly, it may take longer to reduce the levels of IFN-α in the blood.

Administration of hydroxychloroquine did not significantly reduce the CRP levels in this study. Laboratory markers for increased disease activity, such as anti-dsDNA

Table 1. Subject characteristics.

Variable	Treatment Group (Hydroxychloroquine) (n=26)	Control Group (n=29)	*p*-value
Age (year), mean±SD	33.00±10.53	34.55±8.15	0.828§
Education levels, n (%)			
Elementary school	3 (11.54 %)	5 (17.24 %)	0.587‡
Junior high school	5 (19.23 %)	5 (17.24 %)	
Senior high school	10 (38.46 %)	11 (37.93 %)	
Diploma degree	1 (3.85 %)	3 (10.35 %)	
Graduate degree	7 (26.92 %)	5 (17.24 %)	
Duration of SLE (months), median (min-max)	30 (0-138)	40 (0-163)	0.840‡
Duration of SLE treatment (months), median (min-max)	30 (0-138)	40 (0-163)	0.840‡
Type of medication history, n (%)			
MP 4mg/qd	10 (38.5%)	17 (58.6%)	0.140‡
MP 4mg/bid	12 (46.2%)	9 (31.0%)	
MP 4mg/tid	0 (0%)	1 (3.4%)	
MP 4mg/q2d	0 (0%)	1 (3.4%)	
MP 4mg/q3d	1 (3.8%)	0 (0%)	
Without MP	3 (11.5%)	1 (3.4%)	
Type of DMARD history, n (%)			
AZA	6 (23.1%)	6 (20.7%)	0.507‡
AZA and MTx	1 (3.8%)	2 (7.0%)	
CsA	6 (23.1%)	9 (31.1%)	
CsA and MPA	1 (3.8%)	0 (0%)	
CsA and MTx	4 (15.5%)	3 (10.3%)	
MMF	1 (3.8%)	0 (0%)	
MPA	6 (23.1%	6 (20.7%)	
MTx	0 (0%)	1 (3.4%)	
MTx and MPA	1 (3.8%)	1 (3.4%)	
Without DMARD	0 (0%)	1 (3.4%)	
BMI (kg/m^2)			
Pre-test, median (min-max)	21.45 (17.10-32.40)	22.6 (16.40-27.30)	0.835‡
Post-test, mean±SD	21.98±3.58	22.66±2.80	0.430§
SLEDAI, median (min-max)			
Pre-test	5 (0-10)	4 (0-10)	0.593‡
Post-test	4 (0-12)	2 (0-14)	0.124‡
Systolic blood pressure (mmHg), mean±SD			
Pre-test	118.08±13.28	115.41±15.88	0.506§
Post-test	119.73±16.87	117.86±13.05	0.646§
Diastolic blood pressure (mmHg), mean±SD			
Pre-test	73.38±9.22	73.76±11.93	0.898§
Post-test	75.62±13.6	75.48±10.47	0.968§
Total cholesterol (mg/dL), mean±SD			
Pre-test	184.08±39.67	161.23±79.87	0.381§
Post-test	186.67±32.76	178.77±95.61	0.788§
Triglycerides (mg/dL), median (min-max)			
Pre-test	126 (40-479)	112.5 (30-177)	0.361‡
Post-test	106 (34-319)	103.5 (30-391)	0.662‡
HDL cholesterol (mg/dL), mean±SD			
Pre-test	47.42±11.62	49.55±10.37	0.649§
Post-test	55.92±13.06	51.55±11.36	0.403§
LDL cholesterol (mg/dL), mean±SD			
Pre-test	120.78±38.32	126.43±51.04	0.727§
Post-test	117.41±28.94	126.64±41.05	0.469§
BDI			
Pre-test, mean±SD	15.69±8.44	9.52±5.68	0.003§*
Post-test, median (min-max)	8 (0-24)	4 (0-24)	0.272‡
MoCA-INA			
Pre-test, median (min-max)	23 (17-26)	24 (20-25)	0.307‡
Post-test, mean±SD	25.31±3.55	26.97±1.80	0.039§*

§Tested with Independent T-test, ‡Tested with Mann-Whitney, *significant if $p<0.05$. MP: Methylprednisolone, Aza: Azathioprine, MTX: Methotrexate, cSA: cyclosporine A, MPA: Mycophenolic acid, MMF: Mycophenolate mofetil.

Table 2. The effect of hydroxychloroquine on levels of inflammatory biomarker and MoCA score.

Variable	Treatment Group (Hydroxychloroquine) (n=26)	Control Group (n=29)	*p*-value[a]
IL-6			
Pre-test, median (min-max)	9.65 (2.20-100.20)	14.8 (1.50-88.50)	0.533‡
Post-test, median (min-max)	9.15 (1.20-44.40)	16.9 (1.90-85.80)	0.043‡*
p-value[b]	0.048†*	0.746†	
Delta, median (min-max)	-4.20 ((-77)-35.00)	1.20 ((-39.50)-41.30)	0.032‡*
IL-4			
Pre-test, median (min-max)	61.10(15.70-1028.40)	113.80 (10.0-799.7)	0.833‡
Post-test, median (min-max)	53.70 (5.20-783.30)	74.70 (2.10-693.30)	0.717‡
p-value[b]	0.010†*	0.705†	
Delta, median (min-max)	-9.85((-556)-175.80)	1.70 ((-431.5)-282.7)	0.047‡*
IFN-α			
Pre-test, median (min-max)	8.25 (2.70-137.40)	9.10 (0.10-138.30)	0.966‡
Post-test, median (min-max)	5.85 (1.00-137.40)	13.40 (1.00-69.20)	0.367‡
p-value[b]	0.339†	0.419†	
Delta, median (min-max)	-0.75 ((-36.40)-34.20)	1.00 ((-104.30)-47.20)	0.169‡
CRP			
Pre-test, median (min-max)	0.27 (0.00-1.71)	0.17 (0.00-1.80)	0.474‡
Post-test, median (min-max)	0.13 (0.00-1.44)	0.80 (0.02-1.04)	0.196‡
p-value[b]	<0.001†*	0.011†*	
Delta, median (min-max)	-0.09 ((-1.70)-1.14)	-0.50 ((-1.05)-0.66)	0.800‡
MoCA			
Pre-test, median (min-max)	23 (17-26)	24 (20-25)	0.307‡
Post-test, mean±SD	25.31 ± 3.55	26.97 ± 1.80	0.039§*
p-value[b]	<0.001†*	<0.001†*	
Delta, mean±SD	2.69 ± 2.67	3.55 ± 1.64	0.163§

[a]*p*-value of treatment *vs.* control groups. [b]*p*-value between pre- *vs.* post-test. §Tested with Independent T-test, ‡Tested with Mann-Whitney, †Tested with Wilcoxon, *significant if $p<0.05$.

and hypo-complement are often not accompanied by increased CRP levels. This was due to variations in organ involvement, cytokine profiles, and genetic markers that are very heterogeneous; SLE was not a single-entity disease, and this study involved subjects with low disease activity.(16) Low plasma CRP levels associated with the pathogenesis of SLE can be caused by genetic polymorphisms CRP, cleaning of damaged autoantigens during apoptosis, increased gene expression by IFN-α, and therapeutic success.(16)

Table 3. The correlation between inflammatory biomarkers on MoCA Score from control and treatment groups.

Inflammatory Biomarker	MoCA Score		Conclusion
	p-value	r	
IL-6	0.423	-0.110	Not significant
IL-4	0.402	-0.115	Not significant
IFN-α	0.121	-0.211	Not significant
CRP	0.039*	0.279	Significant, weak positive

Tested with Spearman's correlation, *significant if $p<0.05$.

Previous studies have shown that there was an excessive CRP-lowering gene polymorphism (*rs1205*) detected in SLE patients, explaining the basal condition of low and unresponsive CRP in SLE patients with active disease.(17) This could also be the same explanation in this study that the delta CRP levels did not differ between the pre and post-test groups.

The administration of hydroxychloroquine 200 mg/day for 8 weeks had no significant effect on improving cognitive impairment in SLE patients. There are no other studies that have compared SLE patients with cognitive impairment who were given hydroxychloroquine. However, Memantine, a seronergic and nicotine acetylcholine receptor antagonist, affects the glutamatergic system via N-methyl-D-aspartate (NMDA). This receptor can be given to SLE patients with cognitive dysfunction at a dose of 20 mg per day for 12 weeks using automated neuropsychological assessment metrics (ANAM) scores.(18) The concentration at the target levels is expected to be >500-1,000 ng/mL.(19) In a different study, it was shown that taking aspirin was

Table 4. The correlation between inflammatory biomarkers on Sub-MoCA Score from control and treatment groups.

Sub-MoCA score	IL-6		IL-4		IFN-α		CRP	
	p-value	r	*p*-value	r	*p*-value	r	*p*-value	r
Executive visuospatial	0.455	-0.103	0.094	-0.228	0.157	-0.193	0.199	0.176
Naming	0.522	-0.088	0.855	0.025	0.869	0.023	0.051	-0.265
Attention	0.975	-0.004	0.757	0.043	0.882	0.021	0.688	-0.055
Memory	0.147	-0.198	0.160	-0.192	0.160	-0.192	0.931	0.012
Language	0.838	-0.028	0.679	-0.057	0.959	0.007	0.856	-0.025
Abstraction	0.100	0.224	0.920	-0.014	0.541	0.084	0.064	0.251
Delayed recall	0.340	-0.131	0.723	-0.049	0.083	-0.236	0.333	0.133
Orientation	0.641	0.064	0.923	-0.013	0.626	-0.067	0.109	0.219

Tested with Spearman's correlation, *significant if $p<0.05$.

associated to improved cognitive function, especially in older SLE patients with diabetes. This correlation indicated that cognitive improvement primarily occurred through the pathway of inhibition of thromboxane production.(20)

A prospective cohort design with a follow up for 10 years was conducted to observe changes in cognitive function and inflammatory marker. The result of the study showed that increased IL-6 was a strong predictor of worsening cognitive function.(21) In this present study, hydroxychloroquine reduced IL-6 levels, but did not improve cognitive function due to the 8 weeks observation time for the assessment. Prolonged exposure to IL-6 in the brain has been related to various neuropathological problems. *In vitro* study involving rat hippocampal precursor cells incubated with recombinant IL-6 showed a 50% decrease in neurogenesis and an upgrade in apoptotic cell count. These findings suggest that long-term IL-6 exposure in the brain might negatively affect neurogenesis and neuronal health, thereby indicating cognitive decline.(22) In addition to time, the causes of cognitive impairment are multifactorial and not only caused by inflammatory processes.(21) The result of this study indicated that the CRP levels have weak positive correlation with cognitive function. This result is contrary to the report of previous study that CRP levels did not show a significant relationship with cognitive function due to the different synthesis and secretion mechanisms of each mediator. Adipose tissue secretes IL-6, whereas the liver secretes CRP. The increase in CRP levels probably occurs in the late phase of the cascade of inflammatory process.(21,23)

This study attempted to remove biases that might influence the results, such as age, education levels, duration of SLE, SLEDAI score, blood pressure, lipid profile, BMI, and depression. However, there are still several limitations, including the presence of other uncontrollable variables, such as different genetic polymorphisms. Another limitation is the difficulty of controlling confounding variables, such as accompanying neurological and psychiatric diseases, as well as medications, comorbidities, and psychosocial factors. Further study is needed with a longer treatment time, to examine potential influencing factors, such as differences in genetic polymorphisms, neurological diseases, psychiatric diseases, drugs, comorbidities, and psychosocial factors.

Conclusion

In conclusion, the administration of 200 mg/day of hydroxychloroquine for 8 weeks in SLE patients with cognitive dysfunction together with standard therapy (DMARD and steroids) reduced IL-6 and IL-4 levels but did not affect the MoCA scores, IFN-α and CRP levels.

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Authors Contribution

BS planned the study, collected the data, performed the analysis, and wrote the manuscript. SH and HK were involved in giving critical revision for important intellectual content. BS, SH and IV calculated the experimental data and performed the analysis. All authors read and approved the final manuscript.

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