EFFECTIVITY AND RENAL SAFETY OF CYCLOSPORINE AND METHYLPREDNISOLONE COMBINATION THERAPY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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ABSTRAK

Terapi kombinasi siklosporin dan metilprednisolon merupakan terapi lini kedua yang diberikan pada SLE tipe sedang sampai berat yang tidak memberikan respon pada terapi lini pertama. Dari penelitian-penelitian sebelumnya menjelaskan bahwa kombinasi kedua obat ini mampu menekan aktivitas penyakit SLE, namun perlu diwaspadai terjadinya efek samping gangguan renal. Hingga saat ini masih belum terdapat data penelitian di Indonesia terkait efektivitas dan keamanan renal kombinasi ini dalam dosis di lapangan. Oleh karena itu, dapat dipertimbangkan untuk dilakukan monitoring bagaimana efektivitas dan pengaruhnya terhadap renal kombinasi siklosporin dan metilprednisolon pada pasien SLE. Tujuan penelitian ini adalah untuk mengkaji efektivitas penggunaan kombinasi siklosporin dan metilprednisolon dengan parameter MEX-SLEDAI dan menganalisa keamanan terhadap renal dengan serum kreatinin, ureum, dan proteinuria. Penelitian ini merupakan penelitian observasional cohort dengan cara consecutive sampling dalam rentang waktu empat bulan. Pasien SLE yang mendapatkan kombinasi terapi ini dengan nilai RFT normal, diukur skor MEX-SLEDAI, serum kreatinin, ureum dan proteinuria sebanyak 4 kali, yaitu awal penelitian (bulan ke-0), bulan ke-1, 2 dan 3 penelitian. Masing-masing nilai dianalisa secara deskriptif, dibandingkan dengan nilai normal dan nilai sebelumnya untuk melihat bagaimana kecenderungan perubahannya. Selama empat bulan, didapatkan 9 pasien SLE yang memenuhi kriteria inklusi. Hasil pengukuran skor MEX-SLEDAI bulan ke-3 penelitian, jumlah pasien dengan skor <2 meningkat menjadi 55,6% dari 44,4% pasien pada baseline dan satu pasien (11,1%) terjadi peningkatan serum kreatinin, ureum dan proteinuria. Sehingga dapat disimpulkan pemberian kombinasi siklosporin dan metilprednisolon efektif dan aman pada 88,9% pasien namun menunjukkan gangguan fungsi renal pada 11,1% pasien. ***(FMI 2015;51:156-161)***

Kata kunci: *siklosporin, metilprednisolon, SLE, MEX-SLEDAI, kreatinin, ureum proteinuria*

ABSTRACT

*Cyclosporine and methylprednisolone combination are second line therapy for moderate to severe systemic lupus erythemathosus. Some study suggest that the combination were effective to decrease of systemic lupus erythematosus disease activity. But record from the study, cyclosporine cause nephrotoxicity side effect. Therefore, this study should be considered to monitore therapy effect on disease activity and renal side effect. The aim of this study is to analyze the effect of cyclosporine and methylprednisolone combination therapy on disease activity in systemic lupus erythematosus (SLE) assessed by MEX-SLEDAI and renal side effect assessed by creatinine, ureum and proteinuria. A cohort, observational prospective study was conducted to determine the effect of cyclosporine and methylprednisolone combination therapy on disease activity of SLE and renal side effect of this combination. Patients who met criteria were given cyclosporine and methylprednisolone combination that normally renal function tests. MEX-SLEDAI score, creatinine, ureum and proteinuria were measured for fourth times (one time in one mounth), before study, 1st mounth, 2nd mounth, and 3rd mounth. The study comprised 9 patients SLE were given cyclosporine and methylprednisolone combination that normally renal function tests. All patients were female and had productive age. At 3rd mounth, there was increase patients who had MEX-SLEDAI score <2 (55,6%) and one patient (11,1%) had increase of creatinine, ureum and proteinuria. In conclusion, cyclosporine and methylprednisolone combination therapy showed the effectiveness and safety in 88,9% patients and renal dysfunction in 11,1% patients.****(FMI 2015;51:156-161)***

Keywords: *cyclosporine, methylprednisolone, SLE, MEX-SLEDAI, creatinine, ureum, proteinuria.*

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INTRODUCTION

Systemic lupus erytematosus (SLE), also known as lupus, is an autoimmune disease in which organs and cells undergo damage mediated by tissue – binding autoantibody and immune complexes with broad range of clinical manifestation (Parker & Bruce 2007 ; Hahn 2010). Prevalence rates in lupus are estimated to be as

high as 51 per 100 000 people in the USA. Women are affected nine times more frequently than men (Bertsias 2012).

A major event in development of SLE is excessive and abnormal autoantibody production and the formation of immune complex. It appears that excessive and uncontrolled T cell help in the differentiation and activation of autoantibody forming B cells is probably a final pathway. The activation of B and T cells require stimulation by specific antigens. Self-antigen, such as DNA – protein and RNA – protein complex may induce autoantibody production (Mok & Lau 2003). The basic pathological features of SLE are inflammation and blood vessel abnormalities, which include band or occlusive vasculopathy, vasculitis, and immune complex deposition. The best characteristic organ pathology is in kidney (Mok & Lau 2003).

Cyclosporine and methylprednisolone combination are second line therapy for moderate to severe systemic lupus erythemathosus (Perhimpunan Reumatologi Indonesia 2011). Some study suggest that the combination were effective to decrease of systemic lupus erythematosus disease activity. Cyclosporine was corticosteroid-sparing agents, are added to reduce the risk of long-term toxicity from corticosteroids and reduce significantly of steroids dose (Griffiths 2010). Cyclosporine has a long onset of action (4th – 8th weeks), so was combined with steroids (Lacy 2009).

Cyclosporine is a potent immunosuppressive agent primarily due to its inhibitory effect on calcineurin, which is necessary for the activation of T cells (Ogawa, 2010). But record from the study, cyclosporine cause nephrotoxicity side effect. An increase in serum creatinine can indicate acute cyclosporine nephrotoxicity, but is not a sensitive or an accurate means to detect chronic cyclosporine nephrotoxicity (Griffiths 2010). Therefore, this study should be considered to monitore therapy effect on disease activity and renal side effect.

The MEX SLEDAI is used to measure the disease activity of SLE primarily in developing country, where the facilities for estimation of dsDNA antibodies and C3 complement levels may not be easily or always available. The MEX SLEDAI has been validated against the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the Lupus Activity Criteria Count (LACC) and shown to be as reliable as the SLEDAI (rs = 0.894 vs 0.867) (Khanna et al. 2004). The aim of this study was to analyze the effect of cyclosporine and methylprednisolone combination therapy on disease activity in systemic lupus erythematosus (SLE) assessed by MEX-SLEDAI and renal side effect assessed by creatinine, ureum and proteinuria.

MATERIALS AND METHODS

A cohort, observational prospective study was conducted at Dr. Saiful Anwar Teaching Hospital Malang during Agustus to December 2014. Patient selection based on inclusion and exclusion criteria. Inclusion criteria (1) female and male aged $\geq$ 18 years old diagnosed SLE; (2) received cyclosporine and methylprednisolone combination therapy; (3) had normally renal function tests at baseline; (4) without other immunosuppressant therapy. Patients were excluded for the following reasons: (1) with chronic kidney diseases; (2) consume other nephrotoxicity drugs example aminoglycoside, amphotericin B, long therapy NSAID.

MEX-SLEDAI score, creatinine, ureum and proteinuria were measured for fourth times (one time in one month), before study, 1st month, 2nd month, and 3rd month. Descriptive analyses were performed to determine the MEX-SLEDAI score, creatinine, ureum and proteinuria. Each value was compared with normal and before value to evaluate the change.

RESULTS

The result conducted from Agustus to December 2014, 12 patients were obtained and there were 10 patients who met the inclusion criteria, whereas 1 patient was drop out because disobedient drugs. The study comprised 9 patients are female and had productive age. The most clinical manifestations were mucocutaneous (44,5%), fatique and fever (44,5%), arthritis (44,55) and renal disorders (22,2%). Cyclosporine doses were used 50 mg/day in 8 patients and 100 mg/day in 1 patients. Patient profiles and clinical manifestation of all our lupus patients mentioned in Table 1.

Table 2 showed MEX-SLEDAI score on baseline (before study), 1st month, 2nd month and 3th month. Table 3 showed MEX-SLEDAI score according to remission criteria. Creatinine and ureum were used to evaluate renal function to cyclosporine and methylprednisolone combination therapy. Table 4 showed creatinine and ureum profile in SLE patients. According to the table, there was 1 patient had increase of creatinine and ureum. Table 5 showed proteinuria profile in this study. At 3th month this study, 44,5% patients who had negative proteinuria.

Table 1. Profile and clinical characteristics of the patients before study

Characteristics		Patients (N = 9)	Percent (%)
Sex	Male	0	0
	Female	9	100
Age	<18 years	0	0
	18 – 50 years	9	100
	>50 years	0	0
MEX-SLEDAI score	>5 (clearly active) :		
	13 – 20	1	11.1
	6 – 12	2	22.2
	2 - 5 (probably active)	2	22.2
	0 - <2 (clearly inactive)	4	44.5
Clinical Manifestation*	Lupus Nephritis with		
	Mucocutaneous	3	33.3
	Arthritis	3	33.3
	Fatique. fever	3	33.3
	Renal Disorders	2	22.2
	Lymphopenia	1	11.1
	Vaskulitis	1	11.1
	Non Lupus Nephritis with		
	Mucocutaneous	1	11.1
	Arthritis	1	11.1
	Fever	1	11.1
	Haemolysis	1	11.1
Renal Parameter	Creatinine		
	<1.2	9	100
	≥1.2	0	0
	Ureum		
	≤48.5	9	100
	>48.5	0	0
	Proteinuria		
	(0)	2	22.2
	(+1)	3	33.3
	(+2)	3	33.3
	(+3)	1	11.1
Cyclosporine Dose (in a day)	50 mg	8	88.9
	100 mg	1	11.1
MP Dose *	1 x 4 mg → 0 month	4	44.4
	1st month	4	44.4
	2nd month	6	66.7
	3th month	6	66.7
	1 x 8 mg → 0 month	3	33.3
	1st month	3	33.3
	2nd month	1	11.1
	3th month	1	11.1
	3 x 16 mg →0 month	0	0
	1st month	1	11.1
	2nd month	1	11.1
	3th month	1	11.1
	2 x 16 mg → 1st month	1	11.1
	16 – 12 – 0 mg → 2nd month	1	11.1
	16 – 4 – 0 mg → 3th month	1	11.1

*Note : one patient may have one or more clinical manifestation; one patient may have one or more MP dose.

Table 2. MEX-SLEDAI score profile in SLE patients

MEX-SLEDAI score	Criteria*	Patients (%) Month 0	1	2	3
>5 :	Clearly active				
13 - 20		1 (11.1)	-	-	-
6 - 12		2 (22.2)	3 (33.3)	2 (22.2)	-
2 – 5	Probably active	2 (22.2)	4 (44.5)	4 (44.5)	4 (44.5)
0 - <2	Clearly inactive	4 (44.5)	2 (22.2)	3 (33.3)	5 (55.5)
Total		9 (100)	9 (100)	9 (100)	9 (100)

*Khanna et al. 2004

Table 3. MEX-SLEDAI score according to remission criteria

MEX-SLEDAI	Patients (N = 9) (%) Month 0	1	2	3
Not Remission (Score ≥2)	5 (55.6)	7 (77.8)	6 (66.7)	4 (44.4)
Remission (Score <2)	4 (44.4)	2 (22.2)	3 (33.3)	5 (55.6)

Table 4. Creatinine and ureum profile in SLE patients

Creatinine Value (mg/dL)	Patients (N=9) (%) Month 0	1	2	3	Ureum Value (mg/dL)	Patients (N=9) (%) Month 0	1	2	3
Normal <1,2	9 (100)	8 (88.9)	8 (88.9)	8 (88.9)	Normal ≤48.5	9 (100)	8 (88.9)	8 (88.9)	8 (88.9)
Abnormal ≥1,2	0	1 (11.1)	1 (11.1)	1 (11.1)	Abnormal >48.5	0	1 (11.1)	1 (11.1)	1 (11.1)

Table 5. Proteinuria profile in SLE patients

Proteinuria	Patients (N = 9) (%) Month 0	1	2	3
(0)	2 (22.2)	4 (44.5)	3 (33.3)	4 (44.5)
(+1)	3 (33.3)	1 (11.1)	2 (22.2)	1 (11.1)
(+2)	3 (33.3)	1 (11.1)	3 (33.3)	1 (11.1)
(+3)	1 (11.1)	3 (33.3)	1 (11.1)	3 (33.3)
Total	9 (100)	9 (100)	9 (100)	9 (100)

Effectivity of therapy was decrease of MEX-SLEDAI score or <2. Renal safety was normally creatinine and ureum. Table 6 showed effectivity and renal safety to cyclosporine and methylprednisolone combination therapy.

DISCUSSION

Our study demonstrates that the most patients were lupus nephritis. Based on algorithm, cyclosporine and methylprednisolone combination are second line therapy for moderate to severe systemic lupus erythematosus (Perhimpunan Reumatologi Indonesia 2011). In this study showed that cyclosporine and methylprednisolone therapy were effective decrease MEX-SLEDAI score and increase patients with MEX-SLEDAI score <2 (remission). Based on other study showed that cyclosporine and methylprednisolone combination therapy reduction SLEDAI score within 1st month (Dammaco, 2000).

Table 6. Effectivity and renal safety to cyclosporine and methylprednisolone combination therapy

CsA Dose (mg / day)	MP Dose (mg/day)	Effectivity and Renal Safety Parameters				Note
		Mex-SLEDAI score	Proteinuria	SCr	Ureum	
50	4	Remission	Remission	Normal	Normal	+
	4	Remission	↓(+2 → +1)	Normal	Normal	+
	8	Remission	↑(+2 → +3)	Normal	Normal	+
	8 → 4	↓(4 → 2)	Remain (+2 → +2)	Normal	Normal	+
	32 → 28 → 20	↓(15 → 2)	Remission	Normal	Normal	+
	48	↓(8 → 2)	↑(0 → +3)	Normal	Normal	+
	4	Remission	Remission	Normal	Normal	+
	4	Remain (1 → 2)	Remission	Normal	Normal	+
100	8 → 4	Remission	Remain (+3 → +3)	0.73↑ → 1.92	19.4↑ → 55.7	-
Total Patients with *Outcome* Effective and Safety (%)						8 (88.9)

On other study, during cyclosporine and steroids therapy, the mean flare rate decreased by approximately 60% from 0.26 to 0.10 times patient-year (Ogawa, 2010). Cyclosporine main side effect is nephrotixicity. Our study demonstrated that one patient (11,1%) had renal dysfunction which indicated an increase in creatinine, ureum, and proteinuria. Cyclosporine leads to activation of the renin-angiotensin system (RAS), by both direct effects of cyclosporine on juxtaglomerular cells and indirect effects from the renal vasculature hemodynamic changes (arteriolar vasoconstriction) secondary to decreased vasodilator factors and increased endothelin (Naesens 2009). In addition, cyclosporine induces imbalances in the vasodilator/vasoconstrictor ratio of arachidonic acid metabolites, which ultimately promotes renal vasoconstriction.

The first study nephrotoxicity of cyclosporine 10 mg/kg/day in SLE patients showed 100% patients discontinued the study at 7th weeks therapy because nephrotoxicity (Isenberg, 1981). The second study nephrotoxicity of cyclosporine 10 mg/kg/day in uveitis patients showed 35% patients increase in creatinine >1.6 mg/dL in 1st weeks therapy (Palestine 1984). The other study, cyclosporine 2-3 mg/kg/day showed 70% patients had hypertension, 37% patients had renal dysfunction, and 21% patients discontinued of therapy (Ogawa 2010).

CONCLUSION

Cyclosporine and methylprednisolone combination therapy showed the effectiveness and safety in 88,9% patients and renal dysfunction in 11,1% patients.

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