The Relationship between the Number of Major Organ Involvement and Therapeutic Response of Pulse Dose Methylprednisolone in Systemic Lupus Erythematosus Patients

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ABSTRACT

Background. Systemic Lupus Erythematosus (SLE) requires comprehensive and integrated treatment because it can manifest in various organ systems, both non-major and major organs. Pulse doses Methylprednisolone used as induction therapy, it provides dramatic improvement in prognosis in severe lupus through its nongenomic effects. Not all SLE patients who received pulse dose methylprednisolone therapy gives complete response, several factors may influence the therapeutic response, one of which is thought to influence the difference in therapeutic response is the number of major organ involvement.
Objectives. To determine the relationship between the number of major organ involvement and therapeutic response of pulse dose methylprednisolone therapy in SLE patients at Dr. Sardjito Hospital Yogyakarta.
Methods. This study used a retrospective cross-sectional study. The subjects of this study were adult patients with SLE treated in the internal medicine ward at Dr. Sardjito Hospital Yogyakarta and met the inclusion and exclusion criteria from January 1, 2016 to December 31, 2019. The data on the characteristics of the research subjects were taken from the patient's medical records and laboratory data before giving pulse methylprednisolone.
Results. A total of 88 research subjects were taken from medical records. Patients with major organ involvement 1 experienced more complete response (53.8%), major organ involvement 2 mostly partial response (66.7%), major organ involvement 3 (48.6%) and major organ involvement 4 (53.8%) no response, and major organ involvement 5 (75%) partial response. There is a significant relationship with the number of major organ involvement with therapeutic response $p<0.001$. The correlation coefficient $r=0.382$ means that the more major organ involvement the less therapeutic response. The results of multivariate analysis showed that only the number of major organ involvement had a dominant effect on the therapeutic response, $p=0.001$. Regression coefficient 0.797.
Conclusion. The number of major organ involvement significantly affects the success of pulse dose methylprednisolone therapy in SLE patients.

Keywords. SLE, pulse dose methylprednisolone, major organ involvement, therapeutic response

ABSTRAK

Latar Belakang. *Lupus Eritematosus Sistemik (LES) memerlukan penanganan yang komprehensif dan terintegrasi karena dapat bermanifestasi pada berbagai sistem organ baik itu organ non mayor maupun organ mayor. Metilprednisolon merupakan salah satu terapi LES, dimana pada dosis pulse digunakan sebagai terapi induksi dalam mengatasi kekambuhan aktifitas penyakit dan memberikan perbaikan prognosis yang dramatis pada lupus berat melalui efek nongenomik nya. Tidak semua pasien LES yang mendapatkan terapi*

metilprednisolon dosis pulse mengalami respon komplit, beberapa faktor mungkin mempengaruhi respon terapi tersebut, salah satu yang diduga mempengaruhi perbedaan respon terapi tersebut adalah jumlah keterlibatan organ mayor

Tujuan. *Mengetahui hubungan antara jumlah keterlibatan organ mayor dengan keberhasilan terapi metilprednisolon dosis pulse pada pasien LES di RSUP Dr. Sardjito Yogyakarta.*

Metode. *Penelitian ini menggunakan metode potong lintang (cross sectional study) retrospektif, Subjek penelitian ini yaitu pasien dewasa penderita LES yang dirawat di ruang rawat inap penyakit dalam di RSUP Dr. Sardjito Yogyakarta serta memenuhi kriteria inklusi dan eksklusi. sejak 1 Januari 2016 sampai 31 Desember 2019. data karakteristik subyek penelitian diambil dari data catatan medis pasien dan data hasil laboratorium sebelum dilakukan pemberian pulse metilprednisolon.*

Hasil. *Sejumlah 88 subjek penelitian diambil dari catatan medik. Pasien dengan jumlah keterlibatan organ mayor 1 lebih banyak mengalami respon komplit (53,8%), keterlibatan organ mayor 2 sebagian besar respon parsial (66,7%), keterlibatan organ mayor 3 (48,6%) dan keterlibatan organ mayor 4 (53,8%) tidak respon, dan keterlibatan organ mayor 5 (75%) respon parsial. Ada hubungan yang bermakna jumlah keterlibatan organ mayor dengan respon terapi p<0,001. Koefisien korelasi r=0,382 artinya semakin banyak keterlibatan organ mayor semakin tidak respon terhadap terapi. Hasil analisis multivariat diketahui hanya jumlah keterlibatan organ mayor yang berpengaruh dominan terhadap respon terapi p=0,001. Koefisien regresi 0,797.*

Kesimpulan. *Jumlah keterlibatan organ mayor secara bermakna mempengaruhi keberhasilan terapi metilprednisolon dosis pulse pada pasien LES.*

Kata kunci. *LES, metilprednisolon dosis pulse, jumlah keterlibatan organ mayor, respon terapi*

INTRODUCTION

Systemic Lupus Erythematosus (SLE) requires special attention from clinical appearance to its management which requires comprehensive and integrated treatment.[1] This disease is associated with the deposition of autoantibodies and immune complexes, resulting in tissue damage.[2]

The various manifestations of SLE are often not recognized by medical professionals who deal with these patients. SLE can manifest clinically in various organ systems in the human body, both non-major organs such as skin, joints, eyes and major organs such as kidneys, hematology, gastrointestinal, heart, lung, and central nervous system.[3-9] Proper and complete SLE management will produce good outcomes, prevent various complications, increase the survival of SLE sufferers, prevent unnecessary drug use, and reduce medical costs and utilization of health facilities.[10]

Management of SLE is using corticosteroids, corticosteroids affect T and B lymphocytes, targeting several pathogenic pathways that suppress the production of proinflammatory cytokines and reduce the number of circulating T cells, monocytes, and macrophages, inhibit leukocyte activity in areas of inflammation and exert their effects through both genomic and nongenomic mechanisms.[11,12]

Methylprednisolone is a medium-acting corticosteroid where pulse dose is used as induction therapy to treat recurrence of disease activity and provide a dramatic improvement in prognosis in severe lupus. Pulse dose methylprednisolone is mostly used at a dose of 0.5-1g/day for 3 consecutive days and then gradually reduced according to the therapeutic

response. Pulse dose methylprednisolone is indicated in severe and serious conditions.[1] With either therapy, 3-year survival has increased from 50% in the 1950s to 92% in the last 10 years.[13]

In patients with SLE, improvement or recurrence is clinically significant compared to the previous condition, and can be measured with appropriate measuring instruments. There are several measuring tools to assess therapeutic response, including (1) The Responder Index for Lupus Erythematosus (RIFLE), (2) SLE Responder Index (SRI), (3) SLEDAI-2K Responder Index 50 (SRI 50) where the improvement is at least 50 % believed the clinician could reflect a significant improvement in therapeutic response.[14]

In the management of SLE, there are several factors that can affect the therapeutic response and the prognosis of SLE patients. Failure in therapeutic response indicates that the inflammatory process that occurs remains high even after treatment. In addition, one of the causes of high mortality in SLE is the high activity of the disease which at the same time indicates the high inflammatory process that occurs.[15] Low SLE disease activity is the only major clinical variable that can significantly predict the success of methylprednisolone tapering.[16] Lupus disease activity as measured by the SLEDAI value has a high prognostic value for mortality at 6 months.[14] The SLICC/ACR damage index is an important predictor of mortality, while disease duration is not a predictor.[17] In addition, factors that can influence poor outcome in SLE are black race, azotemia, anemia, antiphospholipid syndrome, failure to initial immunosuppressant therapy, poor renal function.[1]

Several studies have shown that not all SLE patients receiving pulse dose methylprednisolone therapy have a complete response. Some patients who have high activity values have responded to pulse therapy but some have not responded. Several factors may be associated with this difference in therapeutic response. The number of major organ involvement is thought to have a relationship with the difference in response to these therapies. Based on this, the researcher wanted to see whether there was a relationship between the number of major organs involved and the response to pulse dose methylprednisolone therapy in SLE patients.

METHOD

This study used a retrospective cross-sectional design. Samples were obtained from medical records, every patient who met the inclusion criteria was included in the study and excluded according to the exclusion criteria. The research was conducted at the Medical Records Installation of Dr. Sardjito Yogyakarta after the

ethical approval from the Health and Medical Research Ethics Committee, Faculty of Medicine, Gadjah Mada University - Dr. Sardjito Hospital. The study was conducted from June 11, 2021 to July 23, 2021.

The research subjects were adult patients with Systemic Lupus Erythematosus who were treated in the Internal Medicine inpatient unit at Dr. Sardjito Hospital and met the inclusion and exclusion criteria from January 1, 2016 to December 31, 2019. The inclusion criteria in this study were: (1) Patients aged 18 years or older, (2) Patients with Systemic Lupus Erythematosus who were diagnosed by the 1997 American College of Rheumatology (ACR) criteria, (3) Patients who were hospitalized by the Internal Medicine Unit team of Sardjito Hospital, Yogyakarta, (4) Patients have indications to receive pulse dose methylprednisolone therapy, namely severe SLE with SLEDAI values > 12 or MEX SLEDAI > 10. Exclusion criteria in this study are: (1) Patients have treatment for chronic infections with the criteria of using drugs for chronic infections (such as tuberculosis, cytomegalovirus, herpes simplex, herpes zooster, HIV infection, hepatitis B or hepatitis C), (2) Patients have contraindications to pulse dose methylprednisolone, (3) Incomplete medical record data. The independent variable in this study was the number of major organ involvement. The dependent variable in this study was therapeutic response to pulse dose methylprednisolone. Potential confounding variables in this study were baseline SLEDAI MEX values, comorbidities, immunosuppressant treatment, hemoglobin, BMI.

Statistical analysis was performed using the statistical package for social sciences (SPSS) version 23, including univariate, bivariate, Spearman correlation and multivariate analysis. This research has received approval from the Medical and Health Research Ethics Commission, Faculty of Public Health and Nursing, University of Gadjah Mada and permission from the Director of Dr. Sardjito Hospital Yogyakarta.

RESULTS

During the study period, subjects were re-analyzed according to the inclusion and exclusion criteria, it was found that 88 subjects received pulsed methylprednisolone between January 2016 and December 2019.

Table 1 shows that the research subjects were 88 subjects with a mean age of 31.3 years with a range of 18-55 years. The majority of SLE patients were women where the subjects consisted of 82 (93.2%) women and 6 (6.8%) men. The research subjects had a mean BMI of 21.24 ± 4.41 kg/m2. The mean initial hemoglobin before pulse dose methylprednisolone was 8.97 ± 2.87 g/dl and the mean MEX SLEDAI was 14.51 ± 5.16 with a

range of 6 – 22. A total of 43 (48.9%) study subjects had comorbidities. The majority of research subjects had major organ involvement in the form of hematological involvement as many as 58 (65.9%) study subjects, followed by neurological involvement as many as 54 (61.4%) study subjects, then kidney involvement as many as 51 (58.0%) study subjects.

Table 1. Characteristics of research subjects

Variabel		Mean	Median (min – max)	n	%
Age (years)		31.3 ± 8.9	31.0 (18 – 55)		
Sex	Man			6	6.8%
	Woman			82	93.2%
BMI (kg/m2)		21.24 ± 4.41	20.65 (14.2 – 41.6)		
Initial MEX SLEDAI		14.51 ± 5.16	14 (6 – 22)		
Hemoglobin (g/dL)		8.97 ± 2.87	9.1 (2.3 – 15.8)		
Comorbid	Yes			43	48.9%
	No			45	51.1%
Major Organ Involvement					
Neurologic	Yes			54	61.4%
	No			34	38.6%
Renal	Yes			51	58.0%
	No			37	42.0%
Haematologic	Yes			58	65.9%
	No			30	34.1%
Pulmonary	Yes			45	51.1%
	No			43	48.9%
Cardiac	Yes			16	18.2%
	No			72	81.8%
Gastrointestinal	Yes			14	15.9%
	No			74	84.1%
Major Organ Involvement		2.70 ± 1.04	3 (1 – 5)		
Therapeutic response	Complete response			18	20.5%
	Partial response			40	45.5%
	No response			30	34.1%
	- Died			8	9.0%
	- Alive			22	25.0%

Table 2 and Figure 1 shows the relationship between the number of major organ involvement and therapeutic response. Patients with major organ involvement 1 experienced more complete response (53.8%), major organ involvement 2 mostly partial response (66.7%), major organ involvement 3 (48.6%) and 4 (53.8%) unresponsive, and major organ involvement 5 (75%) partial response. Spearman correlation analysis (Table 3) showed a significant relationship

between the number of organ involvement and therapeutic response. The correlation coefficient r=0.382 (weak) means that the more major organ involvement the less therapeutic response.

Table 2. Relationship between the number of major organ involvement and therapeutic response

Major Organ Involvement	Therapeutic response					
	Complete response		Partial response		No response	
	n	%	n	%	n	%
1	7	53.8%	5	38.5%	1	7.7%
2	4	19.0%	14	66.7%	3	14.3%
3	6	16.2%	13	35.1%	18	48.6%
4	1	7.7%	5	38.5%	7	53.8%
5	0	0.0%	3	75.0%	1	25.0%

Table 3. Spearman correlation of the number of major organ involvement with therapeutic response

	Therapeutic response	
	R	*p*
Major Organ Involvement	0,382	<0,001

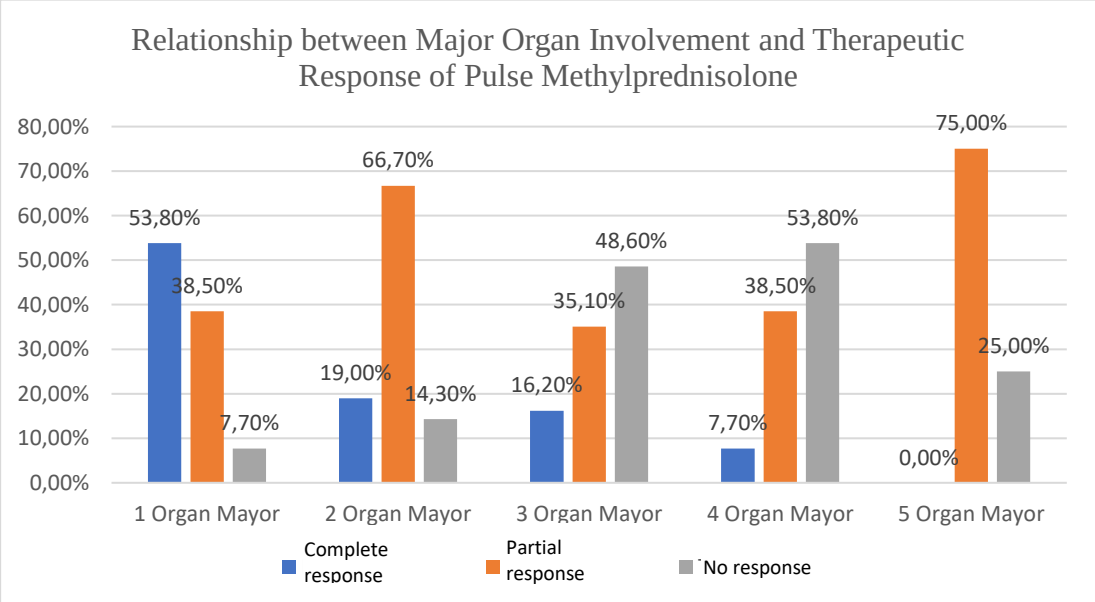

Figure 1. Graphic of Relationship between Major Organ Involvement and Therapeutic Response of Pulse Methylprednisolone

Table 4 shows the bivariate analysis between confounding variables and therapeutic response. Multivariate analysis to examine independent and confounding variables on therapeutic response on

an ordinal scale with the Ordinal Regression Test. Variables that can be continued in the multivariate analysis are variables that have a p value < 0.25, namely the number of major organ involvement, BMI, comorbidities such as thyroid disease, chronic kidney failure, stroke, treatment with azathioprine, mycophenolic acid, chloroquine, cyclophosphamide, Intravenous Immunoglobulin, and methotrexate.

From Table 5, the results of the multivariate analysis showed that only the number of major organ involvement had a dominant effect on the therapeutic response, p=0.009. Regression coefficient of 0.711 (positive) means that the more the number of major organs involved, the less therapeutic response. Meanwhile, BMI, thyroid disease, chronic kidney failure, and stroke were not statistically significant in therapeutic response, as well as treatment using azathioprine, mycophenolic acid, chloroquine, cyclophosphamide, Intravenous Immunoglobulin and methotrexate were also not statistically significant in therapeutic response.

Table 4. Bivariate analysis of confounding variables with therapeutic response

Variabel		Therapeutic response						p
		Complete response		Partial response		No response		
Age (years)		30.83 ± 9.17		32.5 ± 8.91		29.93 ± 8.80		0.481
BMI (kg/m²)		21.57 ± 4.57		21.89 ± 3.61		20.15 ± 5.16		0.248
Hemoglobin		9.48 ± 3.24		9.07 ± 2.82		8.50 ± 2.71		0.507
Initial MEX SLEDAI		13.39 ± 5.05		13.74 ± 4.38		16.17 ± 5.85		0.089
Sex	Man	1	16.7%	2	33.3%	3	50.0%	0.475
	Woman	17	20.7%	38	46.3%	27	32.9%	
Comorbid	Ada	6	14.0%	21	48.8%	16	37.2%	0.335
	No	12	26.7%	19	42.2%	14	31.1%	
Thyroid Disease	Yes	1	50.0%	1	50.0%	0	0.0%	0.215[$]
	No	17	19.8%	39	45.3%	30	34.9%	
Renal Failure	Yes	0	0.0%	5	55.6%	4	44.4%	0.201[$]
	No	18	22.8%	35	44.3%	26	32.9%	
Nephrotic Syndrome	Yes	2	50.0%	1	25.0%	1	25.0%	0.309[$]
	No	16	19.0%	39	46.4%	29	34.5%	
Hypertension	Yes	3	15.0%	10	50.0%	7	35.0%	0.779
	No	15	22.1%	30	44.1%	23	33.8%	
Diabetes mellitus	Yes	0	0.0%	2	50.0%	2	50.0%	0.320[$]
	No	18	21.4%	38	45.2%	28	33.3%	
Stroke	Yes	1	33.3%	2	66.7%	0	0.0%	0.243[$]
	No	17	20.0%	38	44.7%	30	35.3%	
Asthma	Yes	1	50.0%	0	0.0%	1	50.0%	0.856[$]
	No	17	19.8%	40	46.5%	29	33.7%	
Heart Failure	Yes	0	0.0%	4	66.7%	2	33.3%	0.543[$]
	No	18	22.0%	36	43.9%	28	34.1%	
Rheumatoid arthritis	Yes	0	0.0%	3	100.0%	0	0.0%	0.655[$]
	No	18	21.2%	37	43.5%	30	35.3%	

Variabel		Therapeutic response						*p*
		Complete response		Partial response		No response		
Leukemia/lymphoma	Yes	0	0.0%	2	100.0%	0	0.0%	0.717$
	No	18	20.9%	38	44.2%	30	34.9%	
Treatment								
Cyclosporine	Yes	9	19.1%	25	53.2%	13	27.7%	0.268
	No	9	22.0%	15	36.6%	17	41.5%	
Azathioprine	Yes	1	5.0%	11	55.0%	8	40.0%	0.149
	No	17	25.0%	29	42.6%	22	32.4%	
Mofetil mycophenolate	Yes	9	23.7%	18	47.4%	11	28.9%	0.633
	No	9	18.0%	22	44.0%	19	38.0%	
Mycophenolic acid	Yes	7	13.2%	28	52.8%	18	34.0%	0.081
	No	11	31.4%	12	34.3%	12	34.3%	
Chloroquine	Yes	4	16.0%	9	36.0%	12	48.0%	0.222
	No	14	22.2%	31	49.2%	18	28.6%	
Cyclophosphamide	Yes	5	16.7%	19	63.3%	6	20.0%	0.046
	No	13	22.4%	21	36.2%	24	41.4%	
Intravenous	Yes	0	0.0%	2	28.6%	5	71.4%	0.027$
Immunoglobulin	No	18	22.2%	38	46.9%	25	30.9%	
Methotrexate	Yes	2	33.3%	4	66.7%	0	0.0%	0.093$
	No	16	19.5%	36	43.9%	30	36.6%	

Mean±sd: One Way Anova, n(%): Chi-Square, $) Mann Whitney .

Table 5. Multivariat analysis

		Regression coefficients	*P*	CI 95%	
				Lower	Upper
Number of major organ involvement		.711	.009*	.174	1.248
BMI		-.089	.097	-.195	.016
MEX SLEDAI		.062	.194	-.032	.155
Thyroid Disease	Yes	-20.903	.999	-20.903	-20.903
	No				
Renal Failure	Yes	-.578	.488	-2.213	1.057
	No				
Stroke	Yes	-1.026	.407	-3.451	1.399
	No				
Azathioprine	Yes	.482	.388	-.613	1.576
	No				
Mycophenolic acid	Yes	.208	.673	-.761	1.177
	No				
Chloroquine	Yes	.466	.358	-.528	1.459
	No				
Cyclophosphamide	Yes	-.703	.161	-1.685	.280
	No				
Intravenous Immunoglobulin	Yes	1.677	.093	-.282	3.636
	No				
Methotrexate	Yes	-1.269	.155	-3.021	.482
	No				

DISCUSSION

This study assessed the relationship between the number of major organ involvement and the response to pulse dose methylprednisolone therapy in SLE patients at Dr. Sardjito Hospital. Characteristics of study subjects with a mean age of 31.3 years where the subjects consisted of 82 (93.2%) women and 6 (6.8%) men in accordance with the theory that SLE patients were diagnosed between the ages of 15 and 45 years with a ratio of women to men. men for the incidence of SLE is 9:1.8 The mean initial hemoglobin before the pulse dose of methylprednisolone was 8.97 ± 2.87 g/dl. Hematologic manifestations are often found in SLE patients, hematologic abnormalities are found among 83-85% of patients when SLE is diagnosed and most of them are anemia.[1]

In this study, there were 18 patients with complete response (20.5%), 40 partial response (45.5%) and 30 unresponsive (34.1%). Previous studies have shown that giving a pulse dose of methylprednisolone in lupus nephritis patients significantly demonstrated complete remission at 6 months, 12 months, and at the end of the study as indicated by a reduction in the degree of proteinuria in patients after a pulse dose of methylprednisolone.[18] Another study in two groups of SLE patients. who received a high dose of pulsed methylprednisolone (3-5 g/day) compared to a lower dose (1-1.5g/day) were found in both groups, the administration of high-dose and lower-dose methylprednisolone were both effective and significant to decrease the SLEDAI value 6 months post-administration, but increase the risk of infection in both groups, and a significantly higher risk of infection in SLE patients receiving the higher pulse dose of methylprednisolone (p = 0.04).[19] Another study state that a high SLICC/ACR damage index score accompanied by involvement of neuropsychiatric symptoms was independently associated with a poor outcome, while pulsed methylprednisolone and intrathecal injections methotrexate plus dexamethasone is a protective factor against poor outcome.[20] The high value of SLEDAI and SLICC/ACR Damage Index is associated with the increasing number of major organs involved. In this study, there was a significant relationship between the number of major organ involvement and Therapeutic response where the more major organ involvement the less response to pulse dose methylprednisolone therapy.

The mechanism by which pulsed methylprednisolone may affect the difference in therapeutic response is thought that the rapid anti-inflammatory effect of corticosteroids, especially at high doses, is mediated by non-genomic mechanisms.21 The rapid action of non-genomic glucocorticoids is mediated through physical and biochemical interactions with cytosolic receptors

and binding to the membrane.22 Non-genomic glucocorticoid activity can be subclassified into 3 modes of action: non-genomic effects modified by cGCR, non-specific non-genomic effects (e.g., physicochemical interactions with the plasma membrane of high concentrations of glucocorticoids), and effects thought to be mediated by membrane-bound glucocorticoid receptors. The binding of glucocorticoids to the cGCR-associated multi-protein complex causes rapid intercellular signaling via other components such as the co-chaperone src and MAPK. At high concentrations, glucocorticoid molecules enter the cell membrane, which alters cellular function by influencing cation transport through the plasma membrane and by increasing proton leakage from the mitochondria. This leads to a decrease in calcium and sodium cycling through the plasma membrane of immune cells which contributes to the rapid immunosuppression and subsequent reduction of the inflammatory process. The glucocorticoid receptor is expressed on the cell membrane of human cells (mGCR); mGCR-mediated mechanisms are involved in the rapid induction of apoptosis, and the induction of lipomodulin, which inhibits the production of prostaglandins and leukotrienes.[23]

Corticosteroids decrease immune cell function by altering mitochondrial and plasma membranes, and further reduce proinflammatory cytokines by inhibiting arachidonic acid release and through membrane-bound receptors in a transcription-independent process. This pathway may be of particular significance in SLE, as membrane-bound corticosteroid receptors are upregulated on monocytes in SLE patients and are regulated by corticosteroids in a dose-related manner.[21]

Individual therapeutic response varies among SLE patients, with some patients requiring dose increases to achieve an adequate clinical response, this could be attributed to the presence of corticosteroid resistance. Changes in corticosteroid receptor expression are associated with resistance patterns. A small study demonstrated elevated levels of glucocorticoid receptor beta, an inhibitor of corticosteroid action, in patients with high (vs. low) LES disease activity. Specific genetic polymorphisms that correlate with changes in receptor expression and responsiveness have also been identified. Another proposed mechanism for corticosteroid resistance in SLE is intracellular steroid transport outside the cell by membrane transporters. In addition to corticosteroid dose, it is thought that the difference in therapeutic response in SLE patients is the number and type of organs involved in SLE patients. SLE patients with high disease activity that are resistant to steroids exhibit increased lymphocyte expression of the membrane-

associated P-glycoprotein transporter. Overproduction of nuclear factor kappa-B by activated plasmacytoid dendritic cells may be another source of steroid resistance in SLE.[22]

In this study, bivariate confounding analysis was performed for each variable. Variables Hb, age, gender, and the presence of comorbidity did not find a significant correlation to the therapeutic response. When the respective comorbidities and immunosuppressant therapy were described, the variables of nephrotic syndrome, hypertension, diabetes mellitus, heart failure, rheumatoid arthritis, ciclosporin, and mycophenolate mofetil were also not found to be significantly correlated with therapeutic response. The results of multivariate analysis showed that only the number of major organ involvement had a dominant effect on the therapeutic response, p=0.001. Regression coefficient of 0.797 (positive) means that the greater the number of major organs involved, the less therapeutic response.

In this study, there was a significant relationship in bivariate analysis between cyclophosphamide administration and therapeutic response with p value = 0.046, but the results of the ordinal regression multivariate analysis were not significant with p value = 0.161. Another research showed that there was no statistically significant difference in the SLICC damage index value, SLEDAI value, side effects, and mortality in the NPSLE group of patients receiving pulse methylprednisolone therapy compared to those receiving cyclophosphamide. However, the use of cyclophosphamide was associated with a reduced need for prednisone.[24]

This study also found a significant relationship in the bivariate analysis of Intravenous Immunoglobulin administration with therapeutic response with p value = 0.027 but the results of the multivariate ordinal regression analysis test were not significant with p value = 0.093. Immunoglobulin therapy intravenously enhances immunomodulation of autoimmune disease by interacting with various Fcgamma receptors in such a way that it downregulates FcRIIA and FcRIIC activation and/or upregulates inhibitory FcRIIB. In SLE, other mechanisms include inhibition of complement-mediated damage, modulation of cytokine production and cytokine antagonist, modulation of T and B lymphocyte function, induction of apoptosis in lymphocytes and monocytes, downregulation of autoantibody production, manipulation of idiotypic tissues, and neutralization of pathogenic autoantibodies. Intravenous immunoglobulin in SLE is indicated especially in severe cases unresponsive to other treatment modalities, or when SLE can only be controlled with high-dose steroids; so it is useful for sparring agents to save on steroid use.[25]

Determining the number of major organ involvement in the LES is a tool that can be applied to assess the possible response to pulse dose methylprednisolone therapy in the LES during hospitalization, but this study has several limitations: This study has many confounding variables that are not tightly controlled. This study did not see the involvement of minor organs in the LES that might affect the therapeutic response. This study did not include all factors suspected of influencing the therapeutic response in patients. more than the existing data, there are many incomplete patient medical records thus limiting the number of samples that are included.

CONCLUSION

The number of major organ involvement has low correlation ($r < 0.5$) with the response to pulse dose methylprednisolone therapy in Systemic Lupus Erythematosus patients while the more major organs involved the less therapeutic response. Future studies are expected to control confounding variables. A longer follow-up time is needed to see if the number of major organ involvement also affects the therapeutic response after several months of pulse methylprednisolone treatment. Further research with a larger sample is needed to be a better representative of the population.

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