DRUG USE EVALUATION OF CORTICOSTEROIDS IN SYSTEMIC LUPUS ERYTHEMATOSUS OUTPATIENTS

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Abstract

Corticosteroids was the mainstay therapy for SLE, an autoimmune chronic disease. Prolonged use of Corticosteroid caused many side effects' risk. This study was aimed to evaluate corticosteroid drug use in SLE outpatients. This study was conducted on April 2017 to August 2017. Cross sectional design was used and presented with analytical descriptive. The result is, 192 SLE outpatients pass the inclusion criteria and 98,96% are women. Methylprednisolon per oral is the most corticosteroid used for SLE outpatients, combine with 1 other immunosuppressant (65,10 %) and combine with 2 other immunosuppressant (8,33%). From BMI, 26,05% subjects are overweight, perhaps because of corticosteroids side effect, such as weight gain. More than a half SLE outpatients (58,33%) get Calcium supplement and vitamin D3 as prophylactic for osteoporosis because of prolonged use of corticosteroid and 61 SLE outpatients get drug for gastrointestinal use to avoid peptic ulcer. There are 44 cases of potential corticosteroid interaction with other drug that are given together, the most are corticosteroid and aspirin interaction, on 14 patients.

Keywords: corticosteroid, Systemic Lupus Erythematosus, outpatients, drug use evaluation

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic multisystem autoimmune disorder characterized by the development of autoantibodies and immune complexes in various clinical manifestations and tissues damage (Tsang-A-Sjoe and Bultink, 2015). According to Indonesian Lupus Foundation (Yayasan Lupus Indonesia) in the last decade, the SLE patients increases every years. Therefore, proper medication is needed so that the risk of SLE are not fatal and an evaluation of the drugs use in SLE patients is necessary. Morbidity and mortality of SLE patients is still quite high. As many as 40% of SLE deaths occur 12-25 years after being diagnosed, mostly due to infections and complications of chronic steroids and immunosuppressant therapy (Rahman dan Isenberg, 2008).

Corticosteroids and immunosuppressant are the mainstay therapy in SLE cases.

Problems with long-term steroid use such as osteoporosis, the risk of infection, worsen hypertension, provoke diabetes and have an adverse effect on lipid profile which may contribute to increase death from heart disease and the risk of gastrointestinal bleeding (Moroni and Ponticelli, 2017).

Evaluation of corticosteroid use in SLE patients aims to improve the patient's knowledge in carrying out corticosteroid therapy, so that an optimal therapeutic outcome will be obtained. Evaluation of drug use in SLE patients has been done (Setiawati, 2013), but not focused on corticosteroids and the number of subjects of that study was very limited, only 18 patients. This study evaluated the use of corticosteroids in outpatient SLE patients, with a total of 192 subjects.

Methods

This corticosteroids drug use on *Systemic Lupus Erythematosus* (SLE) outpatients, is

a non experimental research, observational analytical, cross sectional, for SLE outpatients from many hospitals in Indonesia, in April-Augustus 2017 and patients fulfill the entry criterias

The study was approved by the Research Ethic Committee in Public health Faculty Diponegoro University Semarang

The inclusion criteria: patients diagnosed SLE for more than 3 months, got corticosteroids therapy and agree to be the subject of this research.

The Data were analyzed by producing descriptive statistics using *statistical product and service solution* (SPSS) version 16..

Results And Discussion

1. Characteristics of the subjects

Of 222 SLE patients who agree to be the subjects of this research, only 192 (86,49%) who met the entry criteria : being diagnosed more than 3 month and got corticosteroids (table 1). Many SLE patients got corticosteroids therapy, showed that corticosteroids are the mainstay therapy for SLE (Kasturi and Sammaritano, 2016)

Estrogen influence in SLE pathogenetics. Estrogen increased autoimmunity with producing more autoantibody, inhibit Natural Killer cell function, and caused atrophy on thymus gland (Wallace, 2007: 173). According to age, most patients are on 30-40 years, which is in productive age where estrogen are still produced. The amount of SLE patients reduced on elderly women who has menopausal (YLI, 2011).

More than a half of the subjects, are normal (57,81%) according to BMI from WHO, 16,67% are overweight (pre obese) and 9,38 % subjects are obese. Corticosteroid side effects are weight gain (Wung et al., 2008). On table I, we can see that 93,75% patients has been diagnosed more than 1 year, 28 subjects (14,58%) diagnosed more than 10 years. This

showed that SLE is a chronic illness (Gordon and Isenberg, 2016).

2. Corticosteroids usage pattern

Although the use of corticosteroids can cause a number of deaths but its use can not only eliminate symptoms, but also reduce mortality in SLE, so that SLE survival increases (Chatham and Kimberly, 2001). The most used corticosteroid is methylprednisolone, given to 186 patients (96.87%), the remaining 5 patients received prednisone (2.60%) and dexamethasone was given only in 1 patient (0.52%). The prescribed dose of methylprednisolone varies, from 4 mg every other day, to 16 mg twice a day. Corticosteroid dose accuracy cannot be evaluated in this study, because corticosteroid dosing is based on the activity of SLE disease, whereas in this study, there was no measurement of SLE disease activity.

The research of Bitencourt Dias et al, 2011 states that there is no difference between Single corticosteroids and two immunosuppressants in inducing remission in patients with SLE nephritis (Bitencourt Dias et al., 2011). In this study, corticosteroids were given singly in 26.56% of SLE patients and used in combination with other immunosuppressants, as listed in Table II. The most widely used immunosuppressant is mycophenolat mofetil in 54 patients (28.12%), antimalarial hydroxychloroquin in 32 patients (16.67%), azathioprine in 27 patients (14.06%), cyclosporine in 16 patients (8.33%) , methotrexate in 7 patients (3.65%) and sulfasalazine were given in 2 patients (1.04%). The use of corticosteroids along with other antimalarials and immunosuppressants can reduce the dose of corticosteroids, so that side effects that may occur can be reduced (Ruiz-Irastorza et al., 2012).

The use of a single corticosteroid or combination with other immunosuppressants can induce remission in one type of lupus nephritis, podocytopathic lupus, but recurrence is more common in single therapy than in combination therapy (Hu et al., 2015)

Table 1. Qualitative demographic variables of respondents (n=192)

Variables		N	%
age (year)	< 20	7	
	20- < 30	67	
	30 - <40	78	
	40 - <50	33	
	≥ 50	7	
Gender	Male	2	
	Female	190	
BMI	< 18,5	31	
	18,5 - <25	111	
	25 - <30	32	
	30 - < 35	12	
	≥35	6	
Education	Junior high school	10	
	Senior high school	83	
	Bachelor degree	35	
	undergraduate	64	
Occupation	Student	16	
	housewife	73	
	Private employees	42	
	Government employees	11	
	unemployed	15	
	Private employer	35	
Years being diagnosed	< 1	12	
	1 – 5	91	
	6 – 10	59	
	11 – 15	17	
	>15	11	
Status	Married	120	
	Not/un yet married	63	
	Widow/widower	9	

Table 2. Corticosteroid usage pattern

corticosteroid (CS)	N	%
Singly	51	26,56
CS + 1 immunosuppressant	125	65,10
CS + 2 immunosuppressant	16	8,33

3. Other drugs

There are many drugs prescribed for SLE outpatients to counter the adverse effect due to corticosteroids used, which will increase according to dosage and duration administration. The most side effects are musculoskeletal complication such as osteoporosis and myopathy (Ruiz-Irastorza et al., 2012). The other side effect were endocrine manifestation, such as hyperglycemia and weight gain, which is reversible on the tapering but can cause diabetes, obesity, hypertension, hyperlipid and atherosclerosis. Cardiovascular complication, such as myocardial infarction and cardiovascular disease often occurred in SLE. The other side effects are infection, psychological disturbance, peptic ulcer, cataract and glaucoma (Moroni and Ponticelli, 2017).

In this study, only 4 patients (2,08%) received antibiotic, none of whom received antiviral or antiparasitic drugs so that it could be stated that the infection side effect because of corticosteroids used in the study subject were only a few. Different with the study of Youssef et al., 2016, which stated that serious and opportunistic infections can occur in long term corticosteroids use and depend on the dosage. The incidence of osteoporosis due to long term use of corticosteroids although in low doses is the risk of the most common side effect (Ruiz-Irastorza et al., 2012).

Doctors gave Calcium and Vitamin D3 supplements to 112 subject (58,33%) to prevent osteoporosis. The other drugs, also possible to overcome the side effect of corticosteroids, 61 patients (31,77%) get the gastrointestinal drugs (most are proton pump inhibitor) to prevent peptic ulcer, 36 patients (18,75%) get antihypertension drugs (most are Angiotensin Receptor Blocker) cause Corticosteroids can cause sodium retention and increase the blood pressure. Twenty patients (10,42%) get blood thinner (most is aspirin) to prevent atherosclerosis, 13 patients (6,77%) get antihyperlipid (the most statin group), 9 patients (4,69%) got neurotropic vitamin, to

prevent myopathy and 4 patients (2,08%) received oral hypoglycemic (metformin and glymeperid). The other corticosteroids side effects is mental disorder, but in this study, only 4 patients (2,08%) get antidepressive drugs.

4. Drug Interaction

There is some potential interactions on corticosteroid use. Methylprednisolone can decrease simvastatin effect, 6 patients get this two drugs together. This interaction is serious, so it needs to change simvastatin with other lowering cholesterol agents. Methylprednisolone also potentially decrease atorvastatin effect, but atorvastatin can increase methylprednisolone level, so can increase the side effect risk, found in 5 patients. The use of methylprednisolone together with aspirin is common, cause SLE patients need blood thinner to prevent atherosclerosis. Interaction between methylprednisolone and aspirin, is at risk of increasing toxicity so can increase the risk of gastrointestinal bleeding (Day et al., 1988). To the SLE patients who receive this drug combinations (14 persons) proton pump inhibitor are prescribed, such as omeprazole and lansoprazole, to prevent the occurrence of gastric ulcer. There are also drugs that can increase the effects of corticosteroids, such as atorvastatin and spironolactone, each prescribed with corticosteroids in 4 patients. The use of corticosteroids along with amlodipine and nifedipine, which are present in 9 and 2 SLE patients, respectively, will reduce the antihypertensive effect, so that blood pressure monitoring must be routinely performed.

Conclusion

The conclusion of this research is methylprednisolone is the most corticosteroid used in SLE outpatients. Corticosteroids are given in combination with other immunosuppressive agent, the most is mycophenolate mofetil. Most corticosteroids (58,33%) are given together with Calcium and

Vitamin D3 to avoid osteoporosis accidents. On this research, 44 (22,92%) potential interactions were found between corticosteroids and other drugs which given together, the most are between corticosteroids and aspirin, happened in 14 subjects (7,29%).

References

- Bachen EA, Chesney MA, Criswell LA, Prevalence of mood and anxiety disorders in women with systemic lupus erythematosus. *Arthritis Rheum.* 2009 Jun 15; 61(6):822-9.
- Bitencourt Dias, C., Pinheiro, C.C., Malafronte, P., Titan, S., Alves de Brito, G., Gera Abrão, J., Dos Santos Silva, V., Toledo Barros, R., Woronik, V., 2011. Prednisone monotherapy induced remission in a group of patients with membranous lupus nephritis. *Clin. Nephrol.* 76, 57–63.
- Chatham, W.W., Kimberly, R.P., 2001. Treatment of lupus with corticosteroids. *Lupus* 10, 140–147.
- Day, R.O., Harris, G., Brown, M., Graham, G.G., Champion, G.D., 1988. Interaction of salicylate and corticosteroids in man. *Br. J. Clin. Pharmacol.* 26, 334–337.
- Hu, W.X., Chen, Y.H., Bao, H., Liu, Z.Z., Wang, S.F., Zhang, H.T., Liu, Z.H., 2015. Glucocorticoid with or without additional immunosuppressant therapy for patients with lupus podocytopathy: a retrospective single-center study. *Lupus* 24, 1067–1075.
- Kasturi, S., Sammaritano, L.R., 2016. Corticosteroids in Lupus. *Rheum. Dis. Clin.* 42, 47–62. doi:10.1016/j.rdc.2015.08.007
- Moroni, G., Ponticelli, C., 2017. Synthetic pharmacotherapy for lupus nephritis. *Expert Opin. Pharmacother.* 18, 175–186.
- Ruiz-Irastorza, G., Danza, A., Khamashta, M., 2012. Glucocorticoid use and abuse in SLE. *Rheumatol. Oxf. Engl.* 51, 1145–1153.
- Setiawati MCN, 2014, Evaluasi Penggunaan Obat, Pengukuran Aktivitas Penyakit dan Pemberian Konseling Pasien *Systemic Lupus Erythematosus* (SLE), MFI vol 9 No 2, 706-789
- Tsang-A-Sjoe, M.W.P., Bultink, I.E.M., 2015. Systemic lupus erythematosus: review of synthetic drugs. *Expert Opin. Pharmacother.* 16, 2793–2806.
- Wung, P.K., Anderson, T., Fontaine, K.R., Hoffman, G.S., Specks, U., Merkel, P.A., Spiera, R., Davis, J.C., St.Clair, E.W., Mccune, W.J., Stone, J.H., 2008. Effects of Glucocorticoids on Weight Change During the Treatment of Wegener's Granulomatosis. *Arthritis Rheum.* 59, 746–753.
- Youssef, J., Novosad, S.A., Winthrop, K.L., 2016. Infection Risk and Safety of Corticosteroid Use. *Rheum. Dis. Clin. North Am.* 42, 157–176, ix–x.