

Analysis of therapeutic effectiveness and adverse effects of long-term corticosteroids among leprosy patients with reactions: A retrospective cohort study

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Abstract

Objectives: Main therapy for leprosy reactions is 12 weeks corticosteroids according to World Health Organization recommendations, but recovery cannot be achieved and recurrence occurs. Long duration of administration was thought to provide better clinical improvement. Evidence of the efficacy of corticosteroids in leprosy reactions is still lacking, and optimal dose and duration of therapy vary, while the need for long-term high-dose corticosteroids makes it difficult to avoid adverse effects.

Methods: This is a retrospective cohort study analyzing the difference between therapeutic effectiveness and adverse effects of 12 weeks and >12 weeks corticosteroids, involving all new leprosy patients without age restriction, at Cipto Mangunkusumo Hospital and Cakung Community Health Center in Indonesia during 1 January 2015–31 December 2017. Secondary data were collected from medical records, and observations carried out until December 2018. Therapeutic effectiveness was assessed from clinical improvement to corticosteroids discontinuation, without 3 months recurrence after first cycle was completed. Adverse effects were assessed by all corticosteroids-related side effects.

Results: Of 195 patients, 57 (29.2%) used 12 weeks corticosteroids, and 138 (70.8%) for >12 weeks. Effectiveness occurred in 38 (66.7%) of 12 weeks group and 106 (76.8%) of >12 weeks group (relative risk = 0.604, 95% confidence interval = 0.307–1.189, $p = 0.143$). Of 145 patients, adverse effects occurred in 12 (31.6%) of 12 weeks group and 70 (65.4%) of >12 weeks group (relative risk = 0.244, 95% confidence interval = 0.111–0.538, $p < 0.001$). Of 171 adverse effects, 37.4% were mild such as dyspepsia, skin disorders, and lipodystrophy, while 62.6% were severe in the form of neuropsychiatric disorders, eye disorders, cardiovascular disease, gastrointestinal bleeding, metabolic-hormonal abnormalities, and reactivation of infections.

Conclusion: There is no effectiveness difference in the form of clinical improvement without 3 months recurrence, between 12 weeks and >12 weeks corticosteroid, while longer administration causes 4 times more events.

Keywords

Leprosy reactions, corticosteroids, recurrence, therapeutic effectiveness, adverse effects

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Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*, which attacks peripheral nerves, skin and upper respiratory tract, and then other organs.^{1,2} Leprosy, mainly found in the tropics, is one of infectious diseases that is not completely controlled. Indonesia is a country that has not been free from the disease, shown by the fact that there are still number of new cases found. New cases of leprosy in the world in 2011 were 219,075, and of these, the most were found in

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Southeast Asia with the highest number in India and then Indonesia. Thus, Indonesia currently ranks the third most cases of leprosy in the world after India and Brazil. Globally, there was a decrease in new case between 2004 and 2011, but Indonesia was not among them.^{2,3} At the end of 2015, the number of people affected by leprosy from 38 World Health Organization (WHO) regional countries was 176,176 or 0.18 cases per 10,000 population. While in Indonesia in 2016, new cases in 34 provinces were 16,826, so the total number of leprosy cases as of April 2017 was 18,200, with a prevalence rate of 0.71 per 10,000 population. This figure indeed shows that Indonesia has reached the status of leprosy elimination, namely, the prevalence <1 per 10,000 population, but the decrease in incidence is still relatively slow.⁴

Leprosy is a public health problem because of the defects, due to inflammation of the nerve tissue that causes damage. One cause of damage to nerve function is leprosy reaction, that is, interruptions with acute episodes in the course of very chronic diseases.³ Leprosy reactions are hypersensitivity reactions, namely, cellular hypersensitivity in type 1 reactions (reversal reactions) and humoral hypersensitivity in type 2 reactions (erythema nodosum leprosum (ENL)).⁵ Reactions can occur before treatment, but especially during or after treatment.³ Both types of reactions can affect 30%–50% of multibacillary (MB) leprosy. Most patients, especially the MB type, experience reactions during the first 6 months of treatment. The exact cause of this reaction is unclear, but it is estimated that a number of triggers play an important role.⁵

The main therapy for leprosy reaction is corticosteroids because of its anti-inflammatory effect,⁵ and as an anti-inflammatory, it is certainly needed in doses higher than physiological doses.⁶ In this case, Indonesian Ministry of Health sets the standard dose given for 12 weeks, according to WHO recommendations. However, severe reactions often have to be treated for 3–6 months while continuing leprosy therapy regimen if it is still in the treatment phase.^{3,5} Some studies do show better results if steroids are given longer. Through WHO standard doses, healing cannot be achieved and recurrence often occurs, while long duration of administration thought to provide better improvement and last longer. A randomized study shows that prednisolone 30 mg reduced in 20 weeks is far better than prednisolone 60 mg reduced in 12 weeks.² Prednisone can even be given at a dose of 0.5–1 mg/kg/day for 6 months–2 years for type 1 reactions and 5–10 years for type 2 reactions,⁷ although other randomized controlled studies conclude that administration of 20 weeks is as effective as 32 weeks, with fewer adverse effects.⁸ Evidence related to the efficacy of corticosteroids in leprosy reactions is lacking, and optimal doses as well as the duration of therapy required also vary greatly, but long-term therapy seems to improve clinical situation.^{7,9}

The need for long-term high-dose corticosteroids in leprosy reactions creates difficulties in avoiding adverse effects, which can cover almost all organ systems because of the ability to affect most organs in the body.¹⁰ Corticosteroids are one of the most common causes of hospital treatment

related to adverse events, and efforts to optimize long-term use of these drugs have been the main focus of various clinical practice guidelines for years.¹¹ It is remarkable that after 70 years of corticosteroid use, there is still uncertainty about how much adverse effects they cause and how they should be monitored.¹² Reports of adverse effects vary, between 7%¹¹ and 33%¹³ on short-term use (<30 days) and 64% if >1 month,¹⁴ even reaching 90% on >2 months use even though the dose is low (≤ 7.5 mg/day).¹⁵ Aside from osteoporosis, only small amount of data are available that can be used to prevent or overcome adverse effects, such as neuropsychiatric disorders or lipodystrophic features and skin disorders, although this situation occurs in nearly 50% patients.¹² In Indonesia, corticosteroid adverse effects in leprosy reactions have not been widely reported. Dermatology outpatient unit at Dr. Sutomo Hospital Surabaya in 2009–2011 reported that this effect was experienced by 8.9% of type 2 leprosy reaction patients.¹⁶

Decision to use corticosteroids requires careful consideration and evaluation of the benefits and risks for each patient. With the differences in the duration of corticosteroid administration in leprosy reactions, while long-term use tends to increase adverse effects, this study retrospectively analyzed the difference in therapeutic effectiveness and incidence of adverse effects between 12 weeks and >12 weeks use of corticosteroid in new leprosy reactions patients at Cipto Mangunkusumo Hospital and Cakung Community Health Center Jakarta for period of 2015–2017, so that the results can be used as consideration for optimizing corticosteroid administration to improve patient safety.

Methods

Study design

This is an observational analytic study with a retrospective cohort design using secondary data from medical records, to assess differences in therapeutic effectiveness and adverse effects between 12 weeks and >12 weeks corticosteroid use in leprosy reactions patients.

Setting

The study was conducted at Cipto Mangunkusumo Hospital and Cakung Community Health Center Jakarta for new leprosy reactions patients from 1 January 2015 to 31 December 2017, which were observed in November–December 2018. Secondary data were collected from the medical records room on the integrated outpatient unit at the hospital based on daily leprosy patient visit reports,^{17–19} and also from leprosy clinic at the Cakung Community Health Center.

Population and sample

Target population is all leprosy patients with reactions, and statistical population is all new leprosy patients who seek

treatment at Cipto Mangunkusumo Hospital and Cakung Community Health Center Jakarta from 1 January 2015 to 31 December 2017. Sample is taken from statistical population that meets inclusion criteria and does not have exclusion criteria. Patients determined as group 1 were taken from all patients who received corticosteroids for 12 weeks, and patients as group 2 were taken from all receiving >12 weeks. Inclusion criteria are patients with diagnosis of leprosy (code A30 according to *International Classification of Diseases, 10th Revision (ICD-10)* classification) accompanied by reaction, which uses corticosteroids as treatment. Exclusion criteria are a discrepancy in the code with the diagnosis recorded in the medical record, history of only 1 time treatment, control or taking corticosteroids irregularly, medical record is illegible, incomplete or cannot be traced, and has used systemic corticosteroids regularly before being diagnosed with leprosy reaction.

This study was planned to use a total sample; however, by calculating using sample size estimation formula for a cohort study, which is a hypothesis test of relative risk, it can be explained as follows

$$n_1 = n_2 = \frac{(Z_{\alpha} \sqrt{2PQ} + Z_{\beta} \sqrt{P_1Q_1 + P_2Q_2})^2}{(P_1 - P_2)^2}$$

By entering P_2 (the proportion of therapeutic effectiveness in 12 weeks corticosteroid group)=0.50²⁰ and RR (relative risk value that is considered significant)=1.5 into the formula, and the value of $\alpha=0.05$ (confidence interval (CI)=95%) and power=80%, then it is found that number of patients required ($n_1=n_2$) is 58 for each group, so that it must involve at least 116 patients.

Variable

The independent variable of this study uses dichotomous nominal scale, namely, leprosy reactions patients using corticosteroids for 12 weeks as group 1 and those using corticosteroids for >12 weeks as group 2. The dependent variable is also a dichotomous nominal scale variable, that is, leprosy reactions patients who experience therapeutic effectiveness and those who do not experience effectiveness. Second are patients who experience corticosteroid adverse effects and those who do not.

Data management

Data collected are secondary data obtained from medical records of new leprosy patients in Cipto Mangunkusumo Hospital and Cakung Community Health Center for the period of 1 January 2015 to 31 December 2017, and observations were carried out until December 2018. All data were recorded in the status of the study on data collection sheets prepared, in the form of

- characteristic/demographic data that include medical record number, name, gender, and age. Patients' identities were changed to group 1 or group 2 research to maintain confidentiality.
- clinical data that include diagnosis, diagnosis information, physical examination (body weight, blood pressure, other generalist and dermatological status), laboratory examination, comorbidities, corticosteroid use (type, dosage, and duration), information on the use of drugs other than corticosteroids, recurrence if any, and adverse effects experienced during the treatment as well as the time they occur.

Data were traced from the time of diagnosis of leprosy, each time of control, when leprosy reactions appear, and data at each time of control thereafter. Data on therapeutic effectiveness in the medical record are assessed from clinical improvement/worsening records, records of gradual decrease of corticosteroids until stopped, presence or absence of recurrences that arise from the record of giving corticosteroids after one cycle therapy is completed, and whether there is a referral to higher health care facilities. Data on corticosteroid adverse effects were assessed from the patient's clinical symptom record, weight gain, increased blood pressure, skin disorders, bone mineral density (BMD) measurements, elevated cholesterol or triglyceride levels, increased blood/urine glucose levels, decreased potassium levels, or consultations with certain medical departments regarding the possibility emergence of adverse effects (psychiatry, ophthalmology, internal medicine, and pediatrics department).

Statistical analysis

Data that have been collected are processed by SPSS version 20.0 with the stages of checking the completeness of filling, grouping and coding, entering into files according to characteristics, entering into SPSS program, and checking again to be ready for analysis. Toward data on basic characteristics of patient (gender, age, leprosy classification, type and onset of reaction), corticosteroid patterns (type and dosage), recurrence (time and frequency), and steroid adverse effects (type, amount, and when it happens), descriptive statistics are presented in the amount (n) and percentage (%). Bivariate analysis was used to assess differences in the therapeutic effectiveness and incidence of adverse effects between the use of 12 weeks and >12 weeks corticosteroids, that is, each through the chi-square (χ^2) test as unpaired categorical comparative hypothesis testing for two groups. Results are considered significant if p value is <0.05 and confidence interval does not exceed number 1. All data that have been analyzed are presented in the form of narrative (textular), images, and tables.

Results

Patient selection process

Since this is a total sampling study, sample is taken from all statistical population that meets inclusion criteria and does

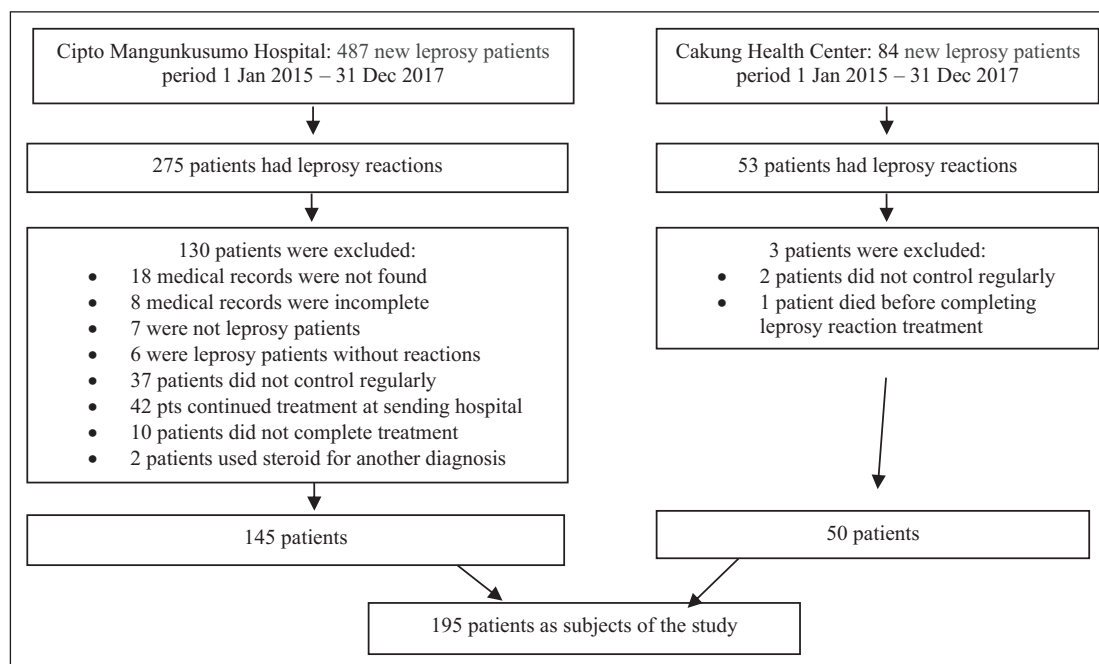


Figure 1. Patient selection flow.

not have exclusion criteria. Through computer database of Cipto Mangunkusumo Hospital medical record unit and daily leprosy patient reports of Tropical Infection Division of Dermatology and Venereology Department, 487 new leprosy patients were found according to ICD-10 classification code A30 during the period of 1 January 2015–31 December 2017. Of these, 275 (56.5%) patients had leprosy reactions, but 130 were excluded for several reasons. From Cakung Community Health Center, 84 new leprosy patients were found during the same period and 53 (63.1%) patients had reactions. Of these, 3 were excluded. Thus, total number of patients that could be included was 195, as shown in Figure 1.

Basic characteristics and patterns of corticosteroid use

Of 195 patients, 57 (29.2%) patients who used corticosteroids for 12 weeks were determined as the first group, and 138 (70.8%) patients who used corticosteroids for >12 weeks as the second group. Basic characteristics and patterns of corticosteroid use can be seen in Table 1.

Leprosy reaction recurrence post corticosteroid therapy

Of 195 patients, 109 (55.9%) patients experienced clinical improvement without recurrence during observation, consisting of 33 (57.9%) people in 12 weeks group and 76 (55.1%) people in >12 weeks group. In both groups, corticosteroids were stopped at different times, as shown in Figure 2.

Meanwhile, 86 (44.1%) patients experienced recurrence after one cycle of steroid therapy. This was experienced by 24 (42.1%) people in 12 weeks group and 62 (44.9%) people in >12 weeks group. Time before recurrence is different between patients, as shown in Figure 3.

With variation in recurrence time, a category consisting of 5 periods is arranged, as shown in Table 2. Recurrence can occur once or more at the same patient, with the most found in this study is four recurrences. In each event, corticosteroids are always given back during periods that also vary.

Corticosteroid adverse effects in patients

Of 195 patients, adverse effect records during corticosteroid therapy were only obtained from Cipto Mangunkusumo Hospital data, which amounted to 145 patients, divided into 38 patients in 12 weeks group and 107 patients in >12 weeks group. Of these, 82 (56.6%) patients experienced adverse effects: 12 (31.6%) people in 12 weeks group and 70 (65.4%) people in >12 weeks group. Adverse effects occur at different times and one patient can experience more than one type of event. All of effects can be seen in Figure 4 and various types that arise in all organ systems are shown in Table 3.

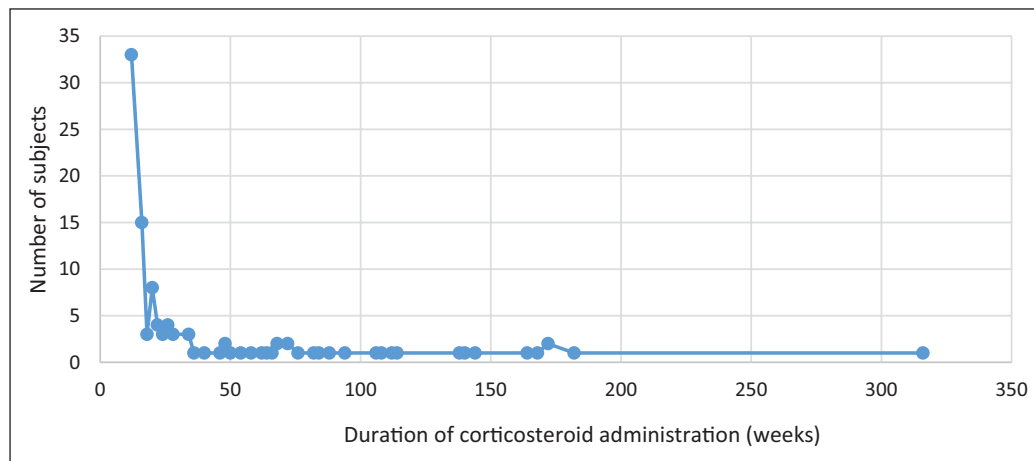
Analysis of differences in therapeutic effectiveness and adverse effects between 12 weeks and >12 weeks corticosteroid use

From the recurrence data, it can be seen a picture of the length of time a patient does not consume corticosteroids after one cycle of treatment is complete. This is related to the effectiveness of therapy, shown in Figure 5.

Table 1. Basic characteristics and patterns of corticosteroid use.

Variable	Total patients, N = 195		12 weeks group, 57/195 (29.2%)		>12 weeks group, 138/195 (70.8%)	
	n/T	%	n/T	%	n/T	%
Gender						
Male	142/195	72.8	36/57	63.2	106/138	76.8
Female	53/195	27.2	21/57	36.8	32/138	23.2
Age						
≤19 years	24/195	12.3	8/57	14.0	16/138	11.6
20–59 years	149/195	76.4	43/57	75.4	106/138	76.8
≥60 years	22/195	11.3	6/57	10.5	16/138	11.6
Leprosy classification						
PB	4/195	2.1	2/57	3.5	2/138	1.4
MB	191/195	97.9	55/57	96.5	136/138	98.6
Type of leprosy reaction						
Type 1 (RR)	152/195	77.9	55/57	96.5	97/138	70.3
Type 2 (ENL)	43/195	22.1	2/57	3.5	41/138	29.7
Onset of leprosy reaction						
Before MDT	103/195	52.8	27/57	47.4	76/138	55.1
During MDT	63/195	32.3	21/57	36.8	42/138	30.4
During RFT	29/195	14.9	9/57	15.8	20/138	14.5
Type of corticosteroid						
Prednisone	57/195	29.2	21/57	36.8	36/138	26.1
Methylprednisolone	137/195	70.3	36/57	63.2	101/138	73.2
Dexamethasone	1/195	0.5	0/57	0.0	1/138	0.7
Initial dose of corticosteroid						
High dose	195/195	100	57/57	100	138/138	100

PB: paucibacillary; MB: multibacillary; RR: relative risk; ENL: erythema nodosum leprosum; MDT: multidrug therapy; RFT: released from treatment.

**Figure 2.** Duration of corticosteroid administration in patients without recurrence.

According to the operational definition that therapeutic effectiveness is a clinical improvement marked by disappearance of leprosy reaction symptoms until steroids are stopped without recurrence within 3 months, then of 195 patients, 144 (73.8%) patients experienced therapeutic effectiveness, consisting of 38 (66.7%) patients in 12 weeks group and 106 (76.8%) patients in >12 weeks group. Regarding the incidence of adverse effects, of 145 patients, 82 (56.6%) patients experienced adverse effects, consisting of 12 (31.6%) patients

in 12 weeks group and 70 (65.4%) patients in >12 weeks group. Results of the analysis can be seen in Table 4.

Discussion

Patient selection process

A number of 195 patients included in this study had met the minimum 116 sample size. Besides Cipto Mangunkusumo

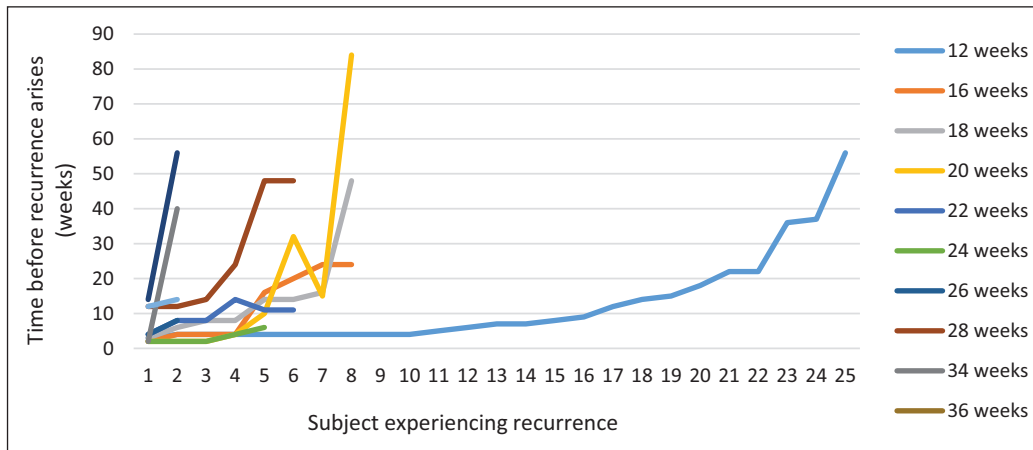


Figure 3. Time before recurrence occurs at various durations of corticosteroid administration.

Table 2. Distribution of leprosy reactions recurrence after corticosteroid therapy.

Recurrence	Total recurrence, 86/195 (44.1%)		12 weeks group, 24/57 (42.1%)		>12 weeks group, 62/138 (44.9%)	
	n/T	%	n/T	%	n/T	%
Recurrence first happened						
≤ 1 month	29/86	33.7	9/24	37.5	20/62	32.3
> 1–3 months	22/86	25.6	10/24	41.7	12/62	19.4
> 3–6 months	19/86	22.1	2/24	8.3	17/62	27.4
> 6 months–1 year	11/86	12.8	1/24	4.2	10/62	16.1
> 1 year	5/86	5.8	2/24	8.3	3/62	4.8
Recurrence frequency						
I	59/86	68.6	17/24	70.8	42/62	67.7
> I	27/86	31.4	7/24	29.2	20/62	32.3

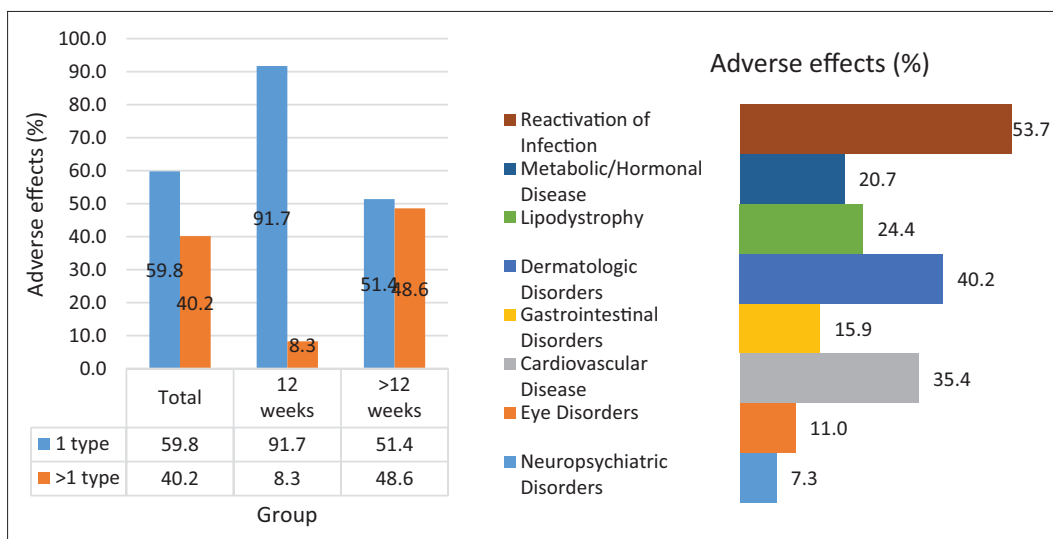


Figure 4. Corticosteroid adverse effects in patients.

Hospital, patients were also taken from Cakung Community Health Center so that in addition to the referral hospital, pattern of corticosteroid administration at first level or primary

health care facilities could also be identified. Only a few exclusion criteria for patient selection were set, with the hope that it would be able to capture the true picture in the

Table 3. Various corticosteroid adverse effects that arise in patients.

Adverse effects	Total, 82/145 (56.6%)	12 weeks group, 12/38 (31.6%)	>12 weeks group, 70/107 (65.4%)	Time happened
Neuropsychiatric disorders	6/82 (7.3%)			
Insomnia	3	1	2	9w, 42w, 2.5y
Convulsion	1		1	12w
Depression	1		1	56w
Psychosis	1		1	4.5y
Eye disorders	9/82 (11%)			
Cataract	5		5	47–48w, 1y, 2y 2m, 3y
Glaucoma	4		4	32w, 48w, 2y, 3y
Cardiovascular disease	29/82 (35.4%)			
Hypertension	27	3	24	1–4w, 6–9w, 11–12w, 16w, 18w, 2.5y, 3y
Heart failure	2		2	42w, 67w
Gastrointestinal disorders	13/82 (15.9%)			
Dyspepsia/acute gastritis	11		11	2w, 4w, 7w, 8w, 10w, 17–18w, 20w, 45w, 67w, 3y
Peptic ulcer	2		2	1y, 2y
Dermatologic disorders	33/82 (40.2%)			
Skin atrophy/striae	6		6	12w, 24w, 34w, 44w, 1y, 1y 7m
Acneiform eruption	21	4	17	4–5w, 8w, 10w, 12–16w, 20w, 24w, 27w
Wound healing damage	6		6	6w, 14w, 22w, 24w, 29w, 49w
Lipodystrophy	20/82 (24.4%)			
Weight gain	9	1	8	6–7w, 11w, 15–16w, 18w, 53w, 82w, 3y
Moon face/buffalo hump/ central obesity	11		11	12w, 15–16w, 22w, 36w, 44w, 1y, 1y 8m, 2y, 3y
Metabolic/hormonal disease	17/82 (20.7%)			
Osteoporosis symptoms	1		1	2.5y
Dyslipidemia	1		1	1y 8m
Hyperglycemia (diabetes mellitus)	6		6	5w, 12w, 32w, 1y 9m, 2y, 3y
Electrolyte disturbance (hypokalemia)	3		3	1y, 1y 9m, 3y
Menstrual disorders	3		3	5w, 15w, 34w
Suppression in child growth and development (short stature and late puberty)	1		1	44w
Suppression of HPA axis (hypocortisol)	2		2	44w, 2y
Infection due to immunosuppression (reactivation of infection)	44/82 (53.7%)			
Pulmonary TB	3		3	20w, 71w, 2y
Bacterial folliculitis/cellulitis	9		9	10w, 24w, 46w, 1y, 1y 3–4m, 2y 2m, 3y
Varicella	1		1	17w
Herpes zoster	3		3	7w, 2y
Herpes simplex	1		1	9w
Hepatitis B	1		1	20w
Parotitis	1		1	20w
Pityriasis versicolor/ candidiasis	22	4	18	2w, 4w, 10w, 12–13w, 18w, 20w, 22–24w, 28w, 43w, 1y 4m, 1y 10m, 2y 2m, 3y
Scabies	3		3	1y 8m, 2y, 4.5y

HPA: hypothalamic–pituitary–adrenal; TB: tuberculosis; w: week; y: year; m: month.

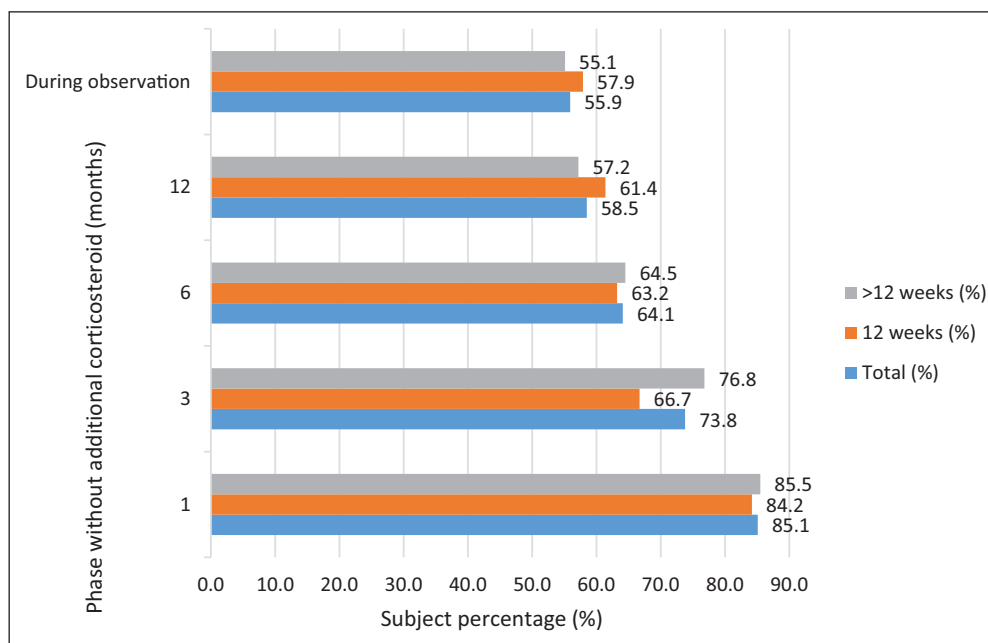


Figure 5. Effectiveness of corticosteroids related to the free period after one cycle treatment.

Table 4. Analysis of differences in therapeutic effectiveness and adverse effects between 12 weeks and >12 weeks corticosteroid use.

Variable	Patients		Analysis	
	12 weeks group, n/T (%)	>12 weeks group, n/T (%)	RR (95% CI)	p value*
Therapeutic effectiveness	38/57 (66.7)	106/138 (76.8)	0.604 (0.307–1.189)	0.143
Adverse effects	12/38 (31.6)	70/107 (65.4)	0.244 (0.111–0.538)	<0.001

RR: relative risk; CI: confidence interval.

*Results of statistical analysis using χ^2 test.

field. Related to the percentage of leprosy reactions found at 57.4%, this is consistent with description that the reaction can affect 30%–50% of MB type leprosy patients.⁵

Basic characteristics and patterns of corticosteroid use

In general, the demographic picture and basic characteristics of patients are similar to data listed in Indonesian health profile. That the majority of leprosy sufferers are male (62.5%), proportion of children leprosy is 11.4%, and the highest classification of leprosy is MB (90.5%)⁴ were also found in this study. This is also in line with results found by Listiyawati et al. in Surabaya that most leprosy sufferers are male (74.1%) and most experienced by patients of productive age (73.2%). Data from Dr. Sutomo Hospital also noted that type of reaction that is more common is type 1 (RR) reaction, which is 86.7%.¹⁶ A different characteristic is the onset of reaction, that is, if it generally occurs during treatment with an MDT (multidrug therapy) regimen or during RFT (released from treatment), this study shows that leprosy reactions most often appear just before treatment. Considering

that Cipto Mangunkusumo Hospital is a referral hospital, a more careful history needs to be taken to ensure whether the patient has never been treated before at primary health care.

Related to corticosteroid use, it appears that the most widely given is methylprednisolone, and then prednisone. Both of these intermediate-acting steroids are indeed suitable for use as anti-inflammatory and immunosuppressive, but according to WHO, prednisone can actually be given as the first choice. Cheap prices are a consideration for use in chronic conditions, except in cases of impaired liver function or water retention.¹⁰ Besides intermediate-acting steroids, dexamethasone is noted to be given to one patient because of the possibility of hypersensitivity to methylprednisolone. Due to its high potential and long-term treatment can cause severe hypothalamic–pituitary–adrenal (HPA) axis suppression, this drug is only used temporarily before being replaced with methylprednisolone again. Regarding the initial dose, most are given in high doses (prednisone equivalent >30–100 mg/day) in accordance with therapeutic guidelines. A medium dose (prednisone equivalent >7.5–30 mg/day) is given to pediatric and some low-weight adult patients, but when calculated based on body weight, all patients are given

the same initial dose of 0.5–1 mg/kg/day, classified as high doses. Although pulse therapy is indicated for severe neuritis, none of patients in this study accepted pulse dose corticosteroid method. A randomized controlled study did not find significant difference between high-dose intravenous methylprednisolone with oral prednisolone compared with a single oral prednisolone,²¹ but further studies are still needed to see the effectiveness of corticosteroids in leprosy reactions when given in immunosuppressant doses.

Usage pattern that turns out to be different between study result with therapeutic guidelines is the duration of corticosteroid administration. Patients who used corticosteroids for >12 weeks were twice as many as those for 12 weeks. Long duration varies greatly, from 4 months to 6 years. This confirms that steroids for leprosy reactions are often reported to be given longer, as of clinical improvement is better and last longer,^{2,20} which will be seen in the next discussion.

Demographics of patients were generally similar between 12 weeks and >12 weeks groups. Gender distribution is indeed more male than female, and proportion is similar in two groups—likewise with age, leprosy classification, reaction onset, steroid type, and initial dose. Characteristic differences were found in reaction type variable that type 2 reactions (ENL) were only slightly found in 12 weeks group (3.5%), while it was quite high (29.7%) in >12 weeks group, in line with literature that states that duration of treatment for RR can reach 2 years, and up to 5–10 years for ENL.⁷ ENL does experience recurrence more often due to many predisposing factors. Most ENL sufferers will experience several episodes of reaction over the years. Frequent relapses and unpredictable trips make ENL relatively difficult to handle.

There is also a difference between corticosteroid administration in Cipto Mangunkusumo Hospital and Cakung Health Center, that is, if clinicians at hospital generally see clinical picture before gradually reducing corticosteroid doses, then in community health center one cycle treatment for 12 weeks is completed first, and then, if it has not improved, will repeat initial dose. Lowering dose too quickly without looking at the clinical picture tends to make corticosteroid duration longer. For this reason, objective guide is needed to assess severity of reaction, which can be used as consideration for determining changes in corticosteroid doses. RR clinical severity scale using scoring system created by Van Brakel^{22,23} is one of methods that can be used, including A score that assesses skin disorders, B score that assesses sensory nerve function, and C score that evaluates motor nerve function. By this system, consideration of increasing corticosteroid dosage will be more measurable, since it correctly adjusts to patient's own clinical condition.

Recurrence event of leprosy reaction post corticosteroid therapy

Compared with the study by Listiyawati et al.¹⁶ which states that only 21.4% of leprosy patients require more than one

cycle therapy, which means experiencing recurrence, the 44.1% total recurrence rate with 42.1% in 12 weeks group and 44.9% in >12 weeks group in this study is quite high. However, Rao et al. in an RCT (randomized controlled trial) comparing three steroid regimens for leprosy reactions reported that proportion of successful treatment without additional steroids after treatment was 54% for 12 weeks duration with 60 mg initial dose, meaning recurrence occurred in 46% of patients, similar to this study. Results look different for categories >12 weeks, that is, recurrence decreased by increasing duration of steroid therapy, namely, 31% for 20 weeks with 30 mg initial dose, and only 24% for 20 weeks with 60 mg initial doses.²⁰ In this study, incidence of recurrence was also high despite the duration of treatment >12 weeks.

As it is well known that the exact cause of hypersensitivity reactions in the form of leprosy reactions for the first time is still unclear, as well as recurrence. A number of risk factors are thought to play an important role as triggers, such as physical and mental stress and accompanying infections caused by bacteria, viruses, or parasites.^{2,3} These trigger factors can be experienced by all patients receiving corticosteroid therapy regardless of duration of treatment, so that the same high recurrence rate for 12 weeks and more is understandable. It also appears that there is no pattern that can be connected between duration of steroid administration with the time of recurrence. Corticosteroid use for 12 weeks can cause recurrences in 4 weeks or 14 months, and 20 weeks corticosteroids also can produce recurrences in 2 weeks or 21 months. If 44 weeks duration can produce steroid-free period in 8 months, administration for 3 years actually results in recurrence in only 2 weeks.

There were indeed some patients who experienced clinical improvement without recurrence and most of them are 12 weeks group. However, it should be remembered that the absence of recurrence is only during the observation period by researcher, which although quite long, it cannot be ascertained that the patient will not experience recurrence in the future. Recurrence can even occur within >1 year, and this study found that after patients stopped taking corticosteroids for 21 months, recurrence reappear.

Corticosteroid adverse effects in patients

With the variation in incidence of corticosteroid adverse effects, which is between 7%¹¹ and 33%¹³ on short-term use (<30 days), 64% if >1 month,¹⁴ 90% on >2 months use,¹⁵ and 8.9% in type 2 leprosy reactions using corticosteroids,¹⁶ then 56.6% found in this study constitutes a new value. The most common adverse effects were reactivation of infection (53.7%), mainly fungal infections; dermatological abnormalities (40.2%) which were mostly in the form of acneiform eruptions; and cardiovascular disease (35.4%) in the form of hypertension. This should be a concern as about 70% of deaths due to Cushing's syndrome are associated with

cardiovascular causes or infections.²⁴ Occurrence time of adverse effects varies, but the 12 weeks group generally only experiences effects that are common at the beginning of steroid therapy, namely, sleep disorders, hypertension, acneiform eruptions, weight gain, and fungal infections. From 171 adverse events that occurred, there were 64 (37.4%) mild effects in the form of dyspepsia, skin disorders, and lipodystrophy. The rest 107 (62.6%) were severe, consisting of neuropsychiatric disorders, eye disorders such as cataracts and glaucoma, cardiovascular disease, gastrointestinal bleeding, metabolic-hormonal abnormalities, and reactivation of infection. Adverse effects that appear the longest are cataracts and glaucoma, suppression of growth and development of children, and suppression of the HPA axis. Overall effect confirms that it may indeed be difficult to avoid adverse effects in various organ systems if corticosteroids are given long term, especially in high dose.^{25–27} Thus to prevent it, any pre-existing comorbid conditions that can increase the risk of adverse effects should be treated before administration begins, and the screening program should be conducted periodically.^{28,29}

Differences in therapeutic effectiveness and adverse effects between 12 weeks and >12 weeks corticosteroid use

The most definite criteria for describing effectiveness of corticosteroid therapy in leprosy reactions are not found, but when viewed in this study, the magnitude of recurrence is not much different between two groups regarding percentages and their appearance in the first 1 month after corticosteroids were stopped. Most patients also experienced only one recurrence, similar in two groups. Difference was seen in the entire time period of recurrence, namely, in 12 weeks group concentrated in ≤ 1 month and > 1 –3 months, while in > 12 weeks group was more scattered, meaning that quite a number of patients had just experienced it in the > 3 –6 months and > 6 months–1 year. On the contrary, high recurrence rate supports the determination in this study that those who experience therapeutic effectiveness are not clinically improved groups without recurrence at all, but rather set limits and then grouped into effective or ineffective, by taking a boundary value of 3 months. It turns out that the analysis shows that there is no difference in effectiveness in the form of clinical improvement without recurrence for 3 months, between 12 weeks and > 12 weeks corticosteroids use, while adverse effects that arise are significantly different, that is, the longer duration of administration causes events 4 times more. Results related to this effectiveness are different from several studies which state that longer duration of steroid administration can provide better improvement and last longer.^{2,7,9} Rao et al. report that prednisolone 20 weeks is much better compared with 12 weeks. However, Wagenaar et al.⁸ reported results similar to this study, that is, there was no effectiveness difference between 20 and 32 weeks

corticosteroids in leprosy reactions, although they did not directly compare with 12-week guidelines recommended by WHO.

Administration of corticosteroids in leprosy reactions is very individual. Although therapies that are considered effective are those that can provide longer phase of clinical improvement without medication, duration of steroid administration cannot be determined in advance. Length of therapy depends on clinical picture and it would be wise to treat based on this condition and patient's response to therapy, which can be achieved if periodic and careful evaluation of clinical symptoms, including signs of recurrence, is carried out. If clinical situation improves, corticosteroid doses can be reduced, while if symptoms persist or even worse, continue or increase the dose. This of course requires good clinical skills from clinicians, that is, besides controlling several factors as trigger of reaction, appropriate and adequate therapy is expected to reduce the possibility of recurrence.² In addition, due to the large likelihood of adverse effects arising in longer corticosteroid administration, and statistically significant, evaluation of therapeutic effectiveness should always be accompanied by evaluation of the occurrence of adverse effects.^{30–34} Costello et al. mentioned in their survey that although clinical weight gain and moon face were not as serious as cardiovascular events, diabetes mellitus (DM), and infections, they were reported as the most important side effects by patients, possibly because they affected quality of life. This must also be considered.³⁵

Limitations and strengths

This study uses secondary data and depends on the notes listed in medical record, so it cannot explore some things that might actually have happened to patient but were not recorded. One of them is the severity of the reaction before starting therapy, which cannot be seen by researcher and was not explained in the medical record. By doing severity grading, it can be seen whether the duration of therapy will be different for each type of reaction, so that in future studies, separate evaluations maybe needed for two types of reactions.

On the contrary, this study uses cohort design, which, although retrospective, can freely trace various clinical changes throughout the course of patient's disease, specifically related to the effectiveness of therapy and side effects. As an observational analytic study, especially with loose inclusion–exclusion criteria and long observation period, this study can reflect real-world data, which is effectively taking a picture of therapeutic characteristics and safety aspects during treatment.³⁶

Conclusion

This study provides several conclusions. First, there is no effectiveness difference between 12 weeks and > 12 weeks corticosteroids use for leprosy reactions, while adverse

effects are significantly different that longer duration causes events 4 times more, where most of these are severe. Second, recurrence of reactions can occur at any time after treatment and does not depend on duration of corticosteroid administration. Thus, it can be suggested that education and training should be given to all health workers in leprosy management, especially in primary health care facilities, one of which is through objective scoring system. This is intended so that all have sufficient competence and are skilled in assessing clinical symptoms to adjust the ups and downs of steroid doses during treatment. In addition, evaluation of therapeutic effectiveness should always be accompanied by assessment of the occurrence of adverse effects. It is necessary to screen for the prevention of these effects from beginning of therapy, followed by periodic examinations covering the entire organ system as indicated. Finally, because of the unpredictable and unpreventable of leprosy reactions while the treatment is very complicated, more research needs to be done about effectiveness of pulse dose steroids methods, triggers for reactions especially non-pharmacological factors such as pregnancy and lactation, vaccination, stress, and infection, and also effective drug for reactions other than corticosteroids, especially if from laboratory examination, there is a suspicion that corticosteroid resistance has developed.

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Ethical approval

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Informed consent

Informed consent was not sought for the present study because this requirement was waived by the Ethics Committee due to data collection method that uses medical records.

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Supplemental material

Supplemental material for this article is available online.

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