Penggunaan Thalidomide pada Pasien Lepra dengan *Erythema Nodosum Leprosum* yang Ketergantungan Steroid: Sebuah Laporan Kasus

(*The Use of Thalidomide in Steroid Dependent Continous Erythema Nodosum Leprosum Leprosy Patient: A Case Report)*

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ABSTRAK

Latar Belakang: Pemberian thalidomide pada kasus eritema nodosum leprosum (ENL) dapat menghambat represi transkripsi dimediasi oleh *tumor necroting factor* (TNF). Thalidomide dapat digunakan sebagai obat pengganti untuk mengurangi ketergantungan steroid. **Tujuan:** Mengevaluasi kasus ENL pada pasien kusta dengan ketergantungan steroid, dan mengetahui efektivitas penggunaan thalidomide sebagai terapi ENL untuk melepaskan ketergantungan steroid. **Kasus:** Pasien kusta tipe *borderline* lepromatosa berusia 39 tahun, dengan riwayat benjolan pada kulit disertai dengan demam, terjadi berulang sejak 4 tahun terakhir jika dosis steroid diturunkan. Pasien mengonsumsi steroid rutin setiap hari selama 4 tahun kembali dan sering disertai demam. Thalidomide 50 mg dua kali sehari dan metil prednisolon 4 mg sekali sehari diberikan pada pasien. Penurunan dosis metil prednisolon konstan dilakukan setiap minggu. Setelah satu bulan terapi, pasien menunjukkan perbaikan yang signifikan. **Pembahasan:** Thalidomide efektif untuk pengobatan ENL, merupakan lini pertama pengobatan ENL karena memberi efektifitas kesembuhan 90% pasien ENL. Pada kasus ini, thalidomide diberikan dan dosis steroid secara perlahan diturunkan sambil diperhatikan keluhan pasien. Setelah pemberian steroid dan thalidomide dihentikan, tidak ada gejala ENL. **Simpulan:** Efektivitas thalidomide di ENL terutama karena aksinya di TNF, tetapi mekanisme lain dapat menyebabkan efek antiinflamasi. Thalidomide efektif dalam pengobatan pasien ENL dengan ketergantungan steroid.

Kata kunci: thalidomide, ketergantungan steroid, metil prednisolon, eritema nodosum leprosum.

ABSTRACT

Background: Treatment thalidomide in erythema nodosum leprosum (ENL), can inhibits the transcription repression mediated by tumor necroting factor (TNF). Thalidomide can be used as sparing agents drug to reduce the dependency of steroid. **Purpose:** To report the effectiveness of thalidomide to treat ENL and of relinquish steroid dependency. **Case:** A 39 years old patient with leprosy borderline lepromatous type, came with complain bumps on skin accompanied with fever, occurring recurrently since 4 years ago if the steroid's dose tappered off. He consumed steroid routinely every day for the last 4 years and if the dose was tapered to 4 mg once daily, the painful bumps reappeared often accompanied by fever. Thalidomide 50 mg twice daily and methyl prednisolone 4 mg once daily was given. The constant tapering off of methyl prednisolone done every week. After a month, the patient shown significant improvement. **Discussion:** Thalidomide is effective in ENL, it is regarded as first line in terms of clinical efficiency because it displays an effect on 90% of ENL patients**.** In this case, thalidomide was given and steroid dose was reduced slowly while observing the clinical manifestation and patient's complain. There were no complain of recurrent ENL after discontinuation of steroid and thalidomide, no serious adverse event happened in this patient as well. **Conclusion:** The effectiveness of thalidomide in ENL is primarily due to its action on TNF but other mechanisms may contribute to its anti-inflammatory effect. Thalidomide is effective in the management of steroid dependent ENL patient.

Key words: thalidomide, steroid dependent, methyl prednisolone, erythema nodosum leprosum

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INTRODUCTION

Severe, chronic, recurrent erythema nodosum leprosum (ENL) is a serious problem. Patients are in need of effective and safe treatment, since there is a great danger that these patients with chronic recurrent ENL become steroid dependent. This may occur even when underlying factors that have been recognized to contribute to establishment of chronic ENL have been

adequately addressed.[1,2]

Erythema nodosum leprosum (ENL, type 2 reaction) complicates lepromatous and borderline lepromatous leprosy and can affect many organ systems, often with irreversible damage. The reaction commonly occur in the 2 years after starting treatment and often run a recurrent or chronic course, sometimes for many years.[3]

Thalidomide is a synthetic glutamic acid derivative first introduced in 1956 in Germany as an over-the counter sedative marketed as Countergan. Initially thought a safe medication, thalidomide was marketed to other industrialized nations by 1958 and was also widely used as an antiemetic by pregnant women. Thalidomide was withdrawn from the world market in 1961 due to occurrences of rare congenital abnormalities, such as phocomelia, in infants born to women who ingested thalidomide during pregnancy. Thalidomide has effects on angiogenesis, immune function and inflammation.[3,4]

Patients with erythema nodosum leprosum (ENL) had unexpected improvement of skin lesions soon after initiating therapy. This discovery triggered a renewal of interest and research into thalidomide. In 1998, the drug was approved by the Food and Drug Administration for ENL. In vitro work has demonstrated that *M. leprae* induced activation of NF-kB in a Schwann cell line leading to transcription repression mediated by TNF is inhibited by thalidomide.[3,4]

There is evidence, however, that thalidomide is effective for treating certain cutaneous conditions. These off-label therapies for thalidomide are not considered first line, but should be considered when the underlying conditions are disabling or disfiguring and recalcitrant to other therapies. Thalidomide has many reported side effects and can lead to birth defects, therefore the usage of this drug need special caution.[4]

A case report of 39 years old patient who was later diagnosed as dependent steroid leprosy is reported. This report discusses how the usage of thalidomide can withdrawal steroid dependency.

CASE REPORT

A 39 years old Javanese man, who has diagnosed from borderline lepromatous type leprosy since 5 years ago, came to the outpatient clinic of Dermatology and Venereology at Dr. Soetomo General Hospital Surabaya with chief complain of recurrent bumps on the skin. This complain accompanied with fever recurrently since 4 years ago if the dose of steroid was decreased, since then he never stop consuming steroid. He currently consumed methyl prednisolone 4 mg daily in the morning and no complaint of bumps, fever and pain in nerve appear when he came.

He started getting multidrugs treatment of leprosy in 2010, routinely control in outpatient clinic and completed leprosy treatment after 12 months. Steroid therapy was given since 2010 for treating leprosy reaction, he firstly got prednisone for few weeks. Since then, he never stop getting steroid agents (prednisone, methyl prednisolone, dexamethasone) with variant doses since he often complaint of bumps and pain with fever that appear whenever the steroid dose was decreased. Few months after the started usage of steroid, patient develop a puffiness around the face and gaining weights.

On general physical examination stated a man, 39 years old, with blood pressure 120/80 mmHg, pulse rate 70 times/minute, respiratory rate 18 times/minute, and body temperature 36.2 degree celcius. There were no sign of anemia, jaundice, cyanotic and respiratory distress found. No enlargement of lymphnodes in cervical area, no abnormality on his thorax, abdominal and extremities was found.

On dermatological examination, the patient currently presented madarosis and facies leonine, also puffiness on region facialis (Figure 1). There were also thickening ear lobes on his auricularis dextra et sinistra (Figure 2). There was deformity in his digiti 1 mannus dextra (Figure 3). Xerosis found in region generalisata without hyperpigmented nor hypopigmented macule (Figure 4).

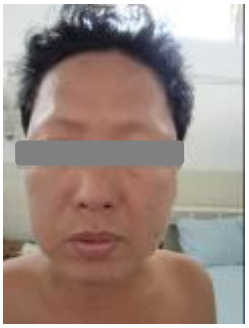


Figure 1. A 39 years old man presenting madarosis, facies leonine, and puffiness around his face.

Figure 2. Both earlobes showed thickening but no nodule or red macule.

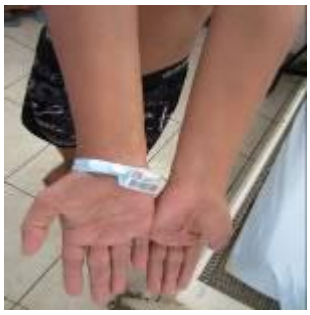
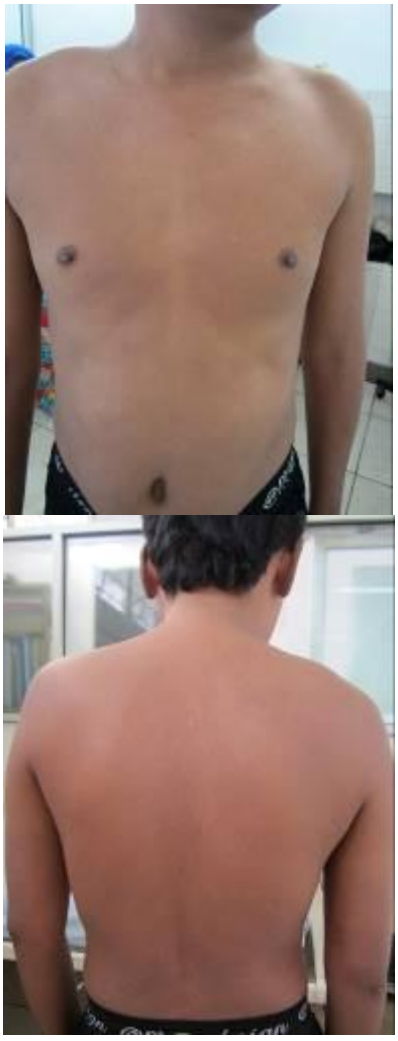


Figure 3. Deformity at his digiti 1 mannus dextra.



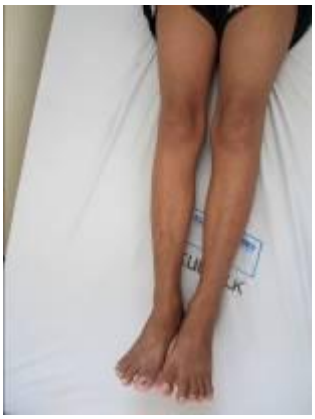


Figure 4. Xerosis on all over body. There is no nodule, no hypopigmented or hyperpigmented macule.

Blood examination was in within normal limit, cortisol serum was 111 mcg/dl. Microscopic examination with acid fast bacilli staining showed the bacterial index was 0%, morphological index 0% (Figure 5). ELISA anti PGL-1 IgM was 3390, IgG: 0.

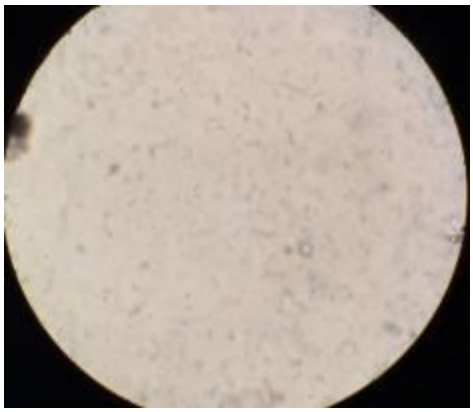


Figure 5. Bacterial index 0%, morphological index 0%.

He started thalidomide on second day of hospitalization, with initial dose of 50 mg two times daily, and he still consumed methyl prednisolone 4 mg daily at morning and will be tapered off slowly. Methyl prednisolone was started to tapered off at day 4 with dose 2 mg daily at morning, and the 10th day he hospitalized, methyl prednisolone tapered off to 2 mg every 2 days. Thalidomide dose was changed on 23rd day into 100 mg a day given at night, on the same day methyl prednisolone given 2 mg every 3 days. After 31 days, methyl prednisolone was stopped and only thalidomide was given, and at day 32 the thalidomide was tapered off to 50 mg daily (consumed at night). Thalidomide 50 mg daily continued, 3 weeks after the thalidomide was stopped.

Any adverse effects and patient's complain was

observed. There were no serious adverse event exist, patient only complain of pain on legs and cramp on both hands, but never appear painful bumps and fever since the methyl prednisolone stop until he discharged from hospital after approximately a month. Other symptomatic treatment also given aneurin, vitamin B complex, and non steroid anti inflamatory drug (NSAID).

Table 1. Clinical progression of patients during hospitalization

Day	Patient's complain	Therapy
Day 1	No bumps, no fever, no pain on nerve	• Thalidomide 2x50mg • Methyl prednisolone 4mg – 0 – 0 • Aneurin 3x1tab • Livron B plex 2x1tab • Emolien
Day 4	Pain on legs (+), bumps(-), fever (-)	• Thalidomide 2x 50 mg (D3) • Methyl prednisolone 2 mg-0-0 • Continue the other drugs
Day 8	Feverish (+), joint pain (+), bumps (-)	• Thalidomide 2x 50 mg (D7) • Methyl prednisolone 2 mg-0-0 (D5) • Continue the other drugs
Day 11	Bumps (-), fever (-), joint pain (-)	• Thalidomide 2x 50 mg (D10) • Methyl prednisolone 2 mg / 2d • Continue the other drugs
Day 15	No bumps, no fever, body pain (+)	• Thalidomide 2 x 50mg (D14) • Methyl prednisolone 2mg/2d (in 6d) • Continue the other drugs
Day19	Body pain (++), bumps(-), fever (-)	• Thalidomide 2x 50 mg (D18) • Methyl prednisolone 2 mg/2d • Natrium diclofenac 2 x 50 mg • Continue the other drugs
Day 23	Body pain (+) ↓, bumps (-), fever (-)	• Thalidomide 2x 50 mg (D22) • Methyl prednisolone 2 mg/3d (D4) • Natrium diclofenac 2 x 50 mg • Continue the other drugs
Day 24	Pain (+), Bumps (-), fever (-)	• Thalidomide 1x 100mg (D23) • Methyl prednisolone 2 mg / 3d (D5) • Continue the other drugs
Day 29	Legs pain (+)↓, cramp on hands and legs(+), bumps (-), fever (-)	• Thalidomide 1x100mg (D28) • Methyl prednisolone 2mg/ 3d (H10) • Natrium diclofenac → aspirin 2 x 1 tab • Continue the other drugs
Day 31	Legs pain (+), cramp on hands and legs(+), bumps (-), fever (-)	• Thalidomide 1 x 100mg (D8) • Methyl prednisolone was stopped • Continue the other drugs

Day	Patient's complain	Therapy
Day 32	Cramp on hands and legs (+)	• Thalidomide 1 x 50mg (D1) • Aspirin 2 x 1 tab • Continue the other drugs
Day 37	Cramps on hand and legs ↓	• Thalidomide 1 x 50mg (D5) • Continue the other drugs • Discharge from hospital

DISCUSSION

Erythema nodosum leprosum occurs most often in lepromatous leprosy type, in up to 75% of cases, but is not rare in borderline lepromatous leprosy patients. These people have high bacterial loads which increasing the risk of ENL. ENL is not erythema nodosum occurring in leprosy, it is a leprosy-specific response, which has some clinical and histologic features in common with erythema nodosum. It may occur before, during, or after the therapy.[5,6]

Type 2 leprosy reaction [or erythema nodosum leprosum (ENL)] is due to an imbalance of humoral immunity and the formation of circulating immune-complexs. The treatment of ENL has been a controversial topic for many years. The drug of choice is thalidomide, although teratogenicity and difficulty in obtaining it restrict its use. This drug is absolutely contraindicated for women during their fertility cycle, even if a contraceptive is being used, because of the interaction between rifampicin and estroprogestine drugs. While corticosteroids are the drugs of choice for ENL leprosy patients suffering from neuritis, or if thalidomide not available (Table 1).[5,7,8]

Table 2. Medical management of reaction states[5]

	Thalidomide	Prednisone or prednisolone	Duration	Other Agents of Unproven Value
Reversal reaction (type 1 reaction)	Of no value	0,5-10 mg/kg Rifampin may increase their catabolism Taper streroid Alternative day treatment may be tolerated	Usually needed for 6 months-2 years May be longer or shorter	Nonsteroid antiinflammatory agent
Erythema nodosum leprosum (type 2 reaction)	The most efficacious drug is available and not contraindicated Initially one dose 100-200 mg qd hs Maintanable dose range 50 mg every other day to 500 mg daily	If thalidomide not available 0,5-10 mg/kg/day	Median duration of treatment is approximately 5 years. Can persist for 10 years	Pentoxyfilin Clofazimine
Lucio phenomenon (usually ceases with use of a antimicrobicidal agents)	Of no value	May be helpful	-	Plasmapheresis reported as helpful in unremitting patient

Short courses of steroids are effective in the management of ENL, they are required if neuritis is present. Sometimes there is difficulty in lowering dose of steroid, even when the dose had lowered to maintenance dose, the clinical manifestation of ENL often recur. A literature stated steroid dependence signified a patient that on tapering the prednisone dose below 10 mg OD, the patients either got new ENLs or had a worsening of their pre-existing ENLs.[1] In this patient who had long term steroid treatment

and got recurrent ENL whenever the steroid dose was tapered off below 10 mg.[9,10]

The side effect of long term use systemic corticosteroid may vary, in dermatological effect can cause thin and fragile skin which also happened in this patient. Facial erythema and puffiness around the face as the other side effect also seen in this case. Striae and acne may occur as the side effect of the long term use systemic corticosteroid, but not occur in this patient.[11]

Steroid dependence is a difficult condition to manage.[9] A clinical experimental performing thalidomide 100 mg daily to release the dependency to steroid in 4 leprosy patients. The average use of steroid in these four patients was 20 mg daily prednisone, if the dose is tappered offf the ENL occur. Thalidomide 100 mg daily was given to these patients and when the clinical manifestation of ENL subsided, steroid did slowly tappered off to 5 mg daily, then the dose of thalidomide also tappered offf until clinical manifestation of ENL does not arise again.[10] In this case, thalidomide was use in the management of steroid dependent ENL patient.

The mechanism of action of thalidomide is incompletely understood but is likely to include inhibition of TNF-α. Thalidomide also inhibits angiogenesis by decreasing basic fibroblastic and vascular endothelial growth factors. Due the immunomodulator and anti tumor necrosis factor-α effect, as well as antiangiogenic, thalidomide is useful for a broad spectrum of inflammatory disorder.[12,13]

Thalidomide is very effective on ENL management, it is regarded as first line in terms of clinical efficiency because it displays some form of an effect on 90% of patients with ENL. The drug's clinical effect can be observed from the first day of use. Subjective symptoms, such as pain and edema, as well as general symptoms such as pyrexia recede so dramatically that the effectiveness of thalidomide is useful as a diagnostic criterion of ENL.[14]

In this case, steroid dose was reduced slowly while observing the clinical manifestation and patient complain. Methyl prednisolone tappered off 2 mg every 3 days if there was ENL occur. Thalidomide dose was 2 times 50 mg as the initial, given at day and night, then once 100 mg at night in day 24 he hospitalized. Methyl prednisolone dose keep tappered off until it was stopped at day 31, and thalidomide dose reduced to once 50 mg a day at the day after the steroid stopped. Thalidomide was finally discontinued after 50 days, and this patient still under our observation.

Controlling ENL by replacing steroids with thalidomide is more difficult than using thalidomide from the beginning. Steroids should be reduced very gradually. It may take some several weeks to reduce the steroids and obtain control with thalidomide alone. Therefore, switching to thalidomide from steroid should be done early.[15]

This drug is derived from glutamic acid, and it has antiemetic, sedative, and hypnotic effect, it is well tolerated and has low toxicity. The following side effects of thalidomide are known teratogenicity, nausea, vomiting, constipation, sedation, swelling in the arms of legs, dizziness, and dryness of the mouth. Teratogenicity is the most important side effect.[16]

In this patient, there was no complain of nausea, vomiting, constipation, but at day 45 he complain of swelling left arm, and we treated with aspirin. No serious adverse event happened in this patient.

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