Guideline for clinical use of thalidomide for management of erythema nodosum leprosum in Japan

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This is the English version of the Guideline on using thalidomide for management of erythema nodosum leprosum in Japan (Jpn J Lepr 80: 275-285, 2011).

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Abstract:
Treatment of erythema nodosum leprosum (ENL, type 2 lepra reaction) with thalidomide is an effective alternative to steroid therapy, but Ministry of Health, Labour and Welfare (Japan) has only approved thalidomide (Thaled® Capsule, Fujimoto Pharmaceutical Corp.) for the treatment of multiple myeloma under the Thalidomide Education and Risk Management System (TERMS®) 2008. Then thalidomide was approved for ENL in 2012 by Ministry of Health, Labour and Welfare. Use of thalidomide for patients with ENL has already been established by various studies in other countries, but limited experience in Japan has hindered application of this medication to domestic patients. This led us to devise a guideline on the usage of thalidomide to treat ENL in Japan. Based on TERMS®, we suggest that administration of thalidomide for ENL should be started at 50-100 mg/day p.o. before going to bed and then the dose should be adjusted according to the patient’s symptoms, while not exceeding the maximum recommended dose of 300 mg/day.

Introduction
In Japan, the treatment of leprosy (Hansen’s disease) has been covered by the national health insurance scheme and performed at general hospitals since the Leprosy Prevention Law was abolished in 1996¹. Type 2 lepra reactions (also known as erythema nodosum leprosum: ENL), which often occur during the treatment of leprosy, are also managed at general hospitals. Under these circumstances, we developed this guideline for the proper use of thalidomide, which is currently thought to be useful for the treatment of ENL based on global data.

The pathophysiology of ENL has not been fully elucidated. There is little clinical experience and no strong evidence supporting the use of thalidomide for ENL, as there has been no clinical trials testing thalidomide for ENL. This guideline presents expert opinion on the use of thalidomide based on best available data in order to support clinical decision of physicians. Physicians are encouraged to adapt their management based on their patient’s clinical presentation.

Thalidomide Education and Risk Management System (TERMS®)¹⁰ must be adhered when using thalidomide in Japan. Furthermore, physicians using thalidomide should always read the “Message from thalidomide victims” at the end of this guideline and keep in mind the lessons learned from the history of thalidomide embryopathy (phocomelia, etc.).

1) Leprosy and lepra reactions
Leprosy is a chronic infection caused by the acid-fast bacterium *Mycobacterium leprae*. Acute inflammatory symptoms that can arise during the course of this disease are called lepra reactions². There are 2 types of lepra reactions, which are type 1 reaction (reversal reaction) and type 2 reaction (ENL) based on different pathophysiology. Type 1 reaction is known to be associated with delayed type hypersensitivity while type 2 reaction is antibody response to *M. leprae*. Both types of reactions may continue for long time and are closely related to peripheral neuropathy and its sequelae, impairment of vision, so it is necessary to make an early diagnosis and provide appropriate treatment.

2) Thalidomide
Thalidomide has a molecular formula of C₁₃H₁₀N₂O₄ and its chemical name is 2-[(3RS)-2,6-dioxopiperidin-3-yl] isoindoline-1,3-dione. It was synthesized in Switzerland in 1953, and was first marketed as a sedative/hypnotic in West Germany in 1957. Thalidomide was also released in Japan in 1958.

It was subsequently found that taking thalidomide during early pregnancy could cause severe birth defects and Grünenthal GmbH (West Germany) initiated a product recall in November 1961. In Japan, sales were stopped and product recall was initiated in September 1962, but some of the products remained on the market after that time. It was reported that there were 309 thalidomide victims in Japan³. An application for marketing thalidomide in the United States (US) was made in 1960, but Food and Drug Administration (FDA) examiner Frances Kelsey questioned its safety and the drug was not approved, at that time. It was fortuitously discovered that thalidomide could improve the symptoms of ENL when patients with leprosy took this drug⁴. In 1998, thalidomide was approved in the US as a treatment for ENL (Table 1), followed by approvals in Australia and New Zealand.

In 1998, thalidomide was also reported to be effective for multiple myeloma⁵, and it was approved for
multiple myeloma by Ministry of Health, Labour and Welfare in Japan in 2008 as Thaled® Capsule (Fujimoto Pharmaceutical Corporation; http://www.fujimoto-pharm.co.jp/index.html). Since thalidomide has a teratogenic effect, physicians, pharmacists and patients must adhere to TERMS® for their use.

3) Efficacy and safety of thalidomide for ENL

There have been no prospective studies on the efficacy of thalidomide for ENL, therefore we should decide on usage of thalidomide from the available data of retrospective investigations (Table 2) [6-14].

Thalidomide was first approved for ENL by US FDA in 1998 (Table 1), where it may be prescribed only by licensed prescribers who are registered in the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S®) program and understand the risk of teratogenicity if thalidomide is used during pregnancy [15]. In Japan, thalidomide was approved for ENL as an expansion of the indication by Ministry of Health, Labour and Welfare in 2012. Corresponding program for S.T.E.P.S® in Japan is called TERMS® which was established by Fujimoto Pharmaceutical Corp. It is absolutely contraindicated for pregnant women based on its teratogenicity. Thus, pregnancy testings are required for female patients with childbearing potential, and male patients must use effective contraception. Patients must adhere to the procedures specified in the TERMS® and give written informed consent. Thalidomide will be prescribed only for these patients and must not be shared with other individuals, even with individuals who have similar symptoms.

4) Diagnosis of ENL

1. Characteristic features of ENL

ENL occurs in patients with the multibacillary (MB) type of leprosy, corresponding to the lepromatous (LL) leprosy and borderline lepromatous (BL) leprosy in the Ridley-Jopling classification. It is more likely to occur in patients with a high bacterial index (BI) among those with MB leprosy. ENL often develops after several months of treatment, but it may occur either before or after treatment.

2. Pathogenesis of ENL

In MB patients, cellular immunity against Mycobacterium leprae antigen is not sufficiently active, so bacteria continue to proliferate. Bacteria are destroyed by antimicrobial treatment or die naturally, and a large amount of bacterial antigens are released into the tissues and bloodstream, leading to production of antibodies. Therefore, immune complexes are formed and deposited in various tissues where complement activation occurs, resulting in damage to tissues and blood vessels.

On histological examination, numerous infiltrating

Table 1 Approval status of thalidomide for type 2 lepra reaction (ENL) in the United States

<table>
<thead>
<tr>
<th>Indications and Usage</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide is indicated for the acute treatment of the cutaneous manifestations of moderate to severe ENL. Thalidomide is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis. Thalidomide is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.</td>
<td>For an episode of cutaneous ENL, thalidomide dosing should be initiated at 100 to 300 mg/day, administered once daily with water, preferably at bedtime and at least 1 hour after the evening meal. Patients weighing less than 50 kg should be started at the low end of the dose range. In patients with a severe cutaneous ENL reaction, or in those who have previously required higher doses to control the reaction, thalidomide dosing may be initiated at higher doses up to 400 mg/day once daily at bedtime or in divided doses with water, at least 1 hour after meals. In patients with moderate to severe neuritis associated with a severe ENL reaction, corticosteroids may be started concomitantly with thalidomide. Steroid usage can be tapered and discontinued when the neuritis has ameliorated. Dosing with thalidomide should usually continue until signs and symptoms of active reaction have subsided, usually a period of at least 2 weeks. Patients may then be tapered off medication in 50 mg decrements every 2 to 4 weeks. Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who flare during tapering, should be maintained on the minimum dose necessary to control the reaction. Tapering off medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks.</td>
</tr>
<tr>
<td>Approval date</td>
<td>July 1998</td>
</tr>
</tbody>
</table>

from Proposed Changes to Approved Thalidomide® Package Insert (Highlight Version) (https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021430lbl.pdf)
Table 2 Use of thalidomide for ENL (1)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study</th>
<th>Number of subjects</th>
<th>Criteria</th>
<th>Intervention</th>
<th>Concomitant drugs</th>
<th>Dosage/administration of THA</th>
<th>Administration period</th>
<th>Evaluation measures</th>
<th>Efficacy results</th>
<th>Safety results</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Double-blind trial</td>
<td>12 subjects (11 men, 1 post-menopausal woman)</td>
<td>ENL (at least 10 months from onset), LL-type</td>
<td>THA or placebo</td>
<td>PSL, aspirin, and</td>
<td>300 mg/day (3 times a day)</td>
<td>After 6 weeks of administration, THA and placebo were switched and administered for another 4 weeks</td>
<td>Evaluate the severity of ENL (body temperature, prescription of other anti-ENL drugs, total leukocyte count)</td>
<td>The dose of PSL was decreased in THA group compared to placebo group. The dose of paracetamol and aspirin were higher in placebo group.</td>
<td>Ovarian: 3 cases (THA: 2 cases, placebo: 1 case), Mild dermatitis (THA: 1 case).</td>
</tr>
<tr>
<td>7</td>
<td>Double-blind trial</td>
<td>52 subjects (37 men, 15 women, 17-58 years old)</td>
<td>Lepromatous patients: Subjects with skin symptoms, neurologic symptoms or other lepra reactions (Nbor EMLike symptoms, reactivation of previous lesions and necrotic lesions of the Lucio phenomenon type, acute neutritis, iritis, induricocytitis, orchitis), Other symptoms (fever, adenopathy, arthralgia, muscle pain, bone pain, abdominal pain, nephritis, hepatosplenomegaly, rhinitis, epistaxis, eating disorder, vomiting, insomnia)</td>
<td>THA or placebo</td>
<td>All other drugs except were prohibited</td>
<td>400 mg/day (4 times a day)</td>
<td>7-28 days</td>
<td>The administration period was varied among subjects. The period and the number of subjects were as follows: 28 days, 25 subjects, 21 days, 13 subjects, 4-7 days, 13 subjects, 7 days, 8 subjects. During the study period, 173 regimens were completed (7 days per regimen) - &quot;complete recovery,&quot; &quot;marked improvement,&quot; and &quot;partial improvement&quot; were 78/85 regimens with THA and 24/58 regimens with placebo (showing a significant difference).</td>
<td>There were no serious side effects. Oedema and nausea were caused by THA. The incidence of gastrointestinal disorders such as dry mouth, constipation, and diarrhoea did not differ significantly between THA and placebo.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Internation multi-center, randomized, double-blind trial</td>
<td>92 subjects (men, 15-80 years old or over)</td>
<td>Lepromatous patients: Acute reaction (BH or EMLike symptoms), Moderate pain is not required (Subjects with other symptoms (fever, obvious neuropathic pain)), Patients with poor performance status were excluded</td>
<td>THA, or aspirin</td>
<td>All other drugs were prohibited</td>
<td>400 mg/day (4 times a day) when the body weight was under 50 kg or over, 6 mg/kg/day (4 times a day) when the body weight was under 50 kg or over. 100-300 mg/day when the body weight was under 50 kg or over. Dosage was determined according to body weight.</td>
<td>7-28 days</td>
<td>If no new acute lepra reaction was observed, the drugs were defined as effective. The symptoms of subject were defined as: Enlarged skin lesions and necrotic lesions observed on the 8th day and who could walk with subacute symptoms, treatment was discontinued until a new acute reaction developed and then was newly administered for 7 days in the case of recovery or non-recovery.</td>
<td>For each of the evaluations on days 8, 15, 22, and 29, the acute reaction was suppressed in 49% by THA and 27% by aspirin.</td>
<td>There were no significant differences in the incidence of the main side effect between THA and aspirin, The incidence of leukopenia was 2% for aspirin and 14% for THA. In addition, dry mouth and nausea were more common with aspirin than THA.</td>
</tr>
<tr>
<td>9</td>
<td>Double-blind trial, Cross-over comparative trial</td>
<td>10 subjects (men, 19-56 years old)</td>
<td>Male</td>
<td>Moderate or severe chronic ENL</td>
<td>THA, or placebo</td>
<td>PSL (15-52.5 mg average 28 mg) or corticosteroids (100 mg)</td>
<td>THA: 300 mg/day</td>
<td>Two studies were conducted: One was for 16 weeks and the other was for 24 weeks.</td>
<td>Evaluate the effectiveness according to dose reduction or steroids.</td>
<td>It was effective in 8 out of 9 subjects examined at 16 weeks. There were some cases of recurrence after discontinuation of THA.</td>
</tr>
<tr>
<td>10</td>
<td>Internation random-controlled trial with the WHO</td>
<td>72 subjects (men)</td>
<td>Male</td>
<td>LL type or recurrent LL-type</td>
<td>CLF or THA</td>
<td>Period A (8 weeks): CLF 300 mg/day, THA, 150 mg/day</td>
<td>Period B (8 weeks): CLF 100 mg/day + DDS 10 mg/day, THA, 50 mg/day + DDS 10 mg/day</td>
<td>Evaluate the severity of lepra reactions and bacteriological examination.</td>
<td>Both CLF and THA were effective for lepra reactions. CLF was better with bacteriological evaluation than THA.</td>
<td>The incidence of total adverse events was 41% in group A (3/12 subjects), 0% in group B (3 cases, 8%).</td>
</tr>
<tr>
<td>11</td>
<td>Randomized double-blind trial</td>
<td>22 subjects (18-46 years old)</td>
<td>Lepromatous patients: Subjects with 10 or more skin nodules, Women, with at least 24 months of amenorrhea or use of surgical contraception, Patients were excluded if they had difficulty in daily life (bedridden), severe neutritis, used THA within 30 days after registration for the trial, or took corticosteroids within 2 weeks after registration for the trial</td>
<td>THA, or placebo</td>
<td>Corticosteroids, aspirin and NSAIDs were prohibited.</td>
<td>After seven days from starting administration, inflammatory lesions were assessed and classified as follows: Complete recovery, no inflammatory lesions (1) Partial recovery, lesions decreased by 50% or more from the level at registration (2) No recovery, Lesions decreased by less than 50% from the level at registration</td>
<td>Complete recovery: Group A: 8 out of 12 subjects, Group B: 8 out of 10 subjects. Partial recovery, Complete + partial recovery: Group A: 12 out of 12 subjects, Group B: 7 out of 10 subjects. There was no difference in effectiveness between Group A and Group B.</td>
<td>The incidence of total adverse events was 90% in group B (9/10 subjects), 52% (2 cases, 20%), headache (2 cases, 20%, drowsiness (2 cases, 40%), skin rash (3 cases, 30%), itching (3 cases, 30%), constipation (1 case, 10%).</td>
<td>Group B had a higher rate of adverse events.</td>
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</tbody>
</table>
neutrophils are found in the dermis and subcutaneous fat. Deposition of immune complexes in the vessel walls may be demonstrated by the immunofluorescent method.

3. Clinical manifestations of ENL

Patients develop high fever and skin nodules accompanied by iritis, neuritis, lymphadenitis, orchitis, arthritis, and refractory proteinuria.  

a. Skin symptoms: The skin develops areas of hardening accompanied by redness that resemble erythema nodosum (EN) and are called ENL. These lesions tend to occur on the lower limbs, but hard erythematous plaques accompanied by tender nodules ranging from bean to egg sizes can affect the whole body (face, limbs, trunk etc.). The lesions often disappear after a few days, but then recur frequently. In severe cases, blisters and abscesses can form and these may burst. Histologically, accumulation of neutrophils can be seen in the subcutaneous fat and the dermis. Polymorphonuclear leukocytes may invade the walls of blood vessels, necrotizing vasculitis may be recognized, and immune complexes may be detected by immunohistochemical staining.

b. Neurologic symptoms: Peripheral neuritis occur and can lead to intolerable pain. In particular, painful swelling of the ulnar nerve is likely to occur, and this often leads to finger deformity during the course of ENL. Attention should be paid to neuralgia, rapid onset of paresthesia and movement disorder, muscle weakness, or gradual progression of neurologic impairment.

c. Eye symptoms: Acute iridocyclitis and scleritis may occur. Hyperemia, eye pain, photophobia, and impaired vision may also occur. Repeated episodes of ENL may lead to chronic iridocyclitis, synchiae, miosis, cataract, secondary glaucoma, and even blindness.

d. Systemic symptoms: Fever, malaise, lymphadenopathy, limb edema, joint pain, and orchitis may accompany ENL.

4. Laboratory findings

There is elevation of neutrophil count, erythrocyte sedimentation rate, CRP, and serum TNF-α level. It has been reported that the serum Zn level decreases. CRP closely reflects disease activity in patients with ENL.

5. Severity of ENL

Depending on the symptoms, the treatment strategy for mild or severe cases is selected. If the main feature of ENL is skin lesions without ulceration and only infiltrated erythema occurs, the condition is considered mild. Mild disease does not

### Table 2 Use of thalidomide for ENL (2)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study</th>
<th>Number of subjects</th>
<th>Entry Criteria</th>
<th>Intervention</th>
<th>Concomitant drugs</th>
<th>Disappearance/administration of THA</th>
<th>Administration period</th>
<th>Outcome measures</th>
<th>Efficacy results</th>
<th>Safety results</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Randomized double-blind trial</td>
<td>44 subjects (men: 18-60 years old, women: at least 49 years old or older (menopause))</td>
<td>Polymicrobial type - Type 2 lepra reaction (EN or EM-like symptoms) - Patients receiving corticosteroid treatment for acute neutritis were excluded</td>
<td>Pentoxifylline or THA</td>
<td>1.2 g of pentoxifylline or 300 mg of THA were administered daily.</td>
<td>30 days</td>
<td>- Body temperature, skin lesions, large lymphadenopathy, other symptoms (nausea, vomiting, weakness, head- ache, arthralgia, muscle pain) were outcome measures. - CRP was measured before and after the study. - The above outcome measures were comprehensively assessed and classified as follows: partial improvement (PI), total improvement (TI), and general improvement (PI + TI = G).</td>
<td>- The residence of side effects at 1 week was 25% for THA and 34.4% for pentoxifylline, while it was 15.8% for THA and 11.1% for pentoxifylline at 3 weeks. There was no significant difference between the drugs at 1 week or 3 weeks.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Randomized controlled trial</td>
<td>60 subjects (49 men, 11 women)</td>
<td>Polymicrobial type - Moderate to severe ENL</td>
<td>THA or PSL</td>
<td>THA 100 mg/day for 1 week. After that, decreased the dose by 50 mg every 2 weeks. - PSL 40 mg/day for 2 weeks. After that, decreased the dose by 10 mg every 2 weeks.</td>
<td>Remission of skin lesions with THA: 5.54 days; PSL: 13.23 days; remission of systemic symptoms with THA: 2.04 days; PSL: 4.17 days; duration of response with THA: 10.92 months; PSL: 2.23 months; recurrence rate with THA: 6.8% (2/28); PSL: 33.3% (10/30); CRP: 33.3% (3/9); THA: 33.3% (1/3); PSL: 33.3% (1/3); CRP: 0.0001.</td>
<td>- Clinical response (remission of skin lesions, remission of systemic symptoms, duration of response), - Recurrence rate</td>
<td>- The incidence of side effects of THA were somnolence (9 cases), constipation (5 cases), and itching (6 cases).</td>
<td></td>
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</tr>
</tbody>
</table>

CLP: clofazimine; DDS: dapsone; EN: erythema nodosum; EM: erythema multiforme; LL: lepromatous; NSAIDs: nonsteroidal anti-inflammatory drugs; PSL: prednisolone; THA: thalidomide; CRP: C-reactive protein; THA: thalidomide; PSL: prednisolone; GI: grade improvement; PI: partial improvement; TI: total improvement; GI: grade improvement; PI: partial improvement; TI: total improvement; THA: thalidomide; PSL: prednisolone.
interfere with daily life.

On the other hand, ulceration of skin lesions and the presence of other symptoms, such as neurologic symptoms, ocular symptoms, and fever, mean that the disease is severe. The symptoms interfere with daily life. Skin ulcers cause persistent scars after they heal, while neurologic and ocular symptoms may evoke permanent sequelae. Therefore, it is important to treat severe ENL early and adequately, taking special care to prevent neuropathy.

The CRP level can also be used for judgment of severity, but there is no specific cutoff value.

5) Treatment of ENL

1. Precautions

The patient need to rest, can work or attend school, depending on the symptom. They should be instructed to avoid drinking alcohol and get enough sleep. If patients develop symptoms of multiple organ symptoms, consider hospital admission for rest.

2. Mild ENL

No specific treatment is required. If patients complain any symptoms of ENL, consider symptomatic treatments. For example, drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) and sedatives may be administered to alleviate pain.

3. Severe ENL

In severe cases, thalidomide or steroid therapy should be considered. Administration of thalidomide to pregnant women is absolutely contraindicated. Furthermore, it is necessary to manage this drug strictly and education of prescribing doctors is mandated by TERMS.®

a. Treatment of ENL with thalidomide: Thalidomide is effective for ENL.® The requirements of TERMS® must be adhered to properly when using thalidomide.

   Usually, thalidomide is administered at a dose from 50 to 100 mg/day before going to bed. If it is effective, symptoms of ENL will begin to improve the following morning, with quick subsiding of fever, induration of the skin, and neuritis. Rapid improvement of symptoms due to oral administration of thalidomide is also helpful for diagnosis of ENL. If thalidomide is ineffective, it is highly likely that the patient does not have ENL, and other conditions should be considered such as a type 1 reaction.

The dose is reduced according to improvement of symptoms, but dose reduction does not require careful tapering as is necessary with steroid therapy. Because ENL may occur repeatedly during the course of leprosy, the dose of thalidomide is increased or decreased according to the changes of symptoms, objective findings, and laboratory findings (CRP level). In Japan, 25 mg capsule of thalidomide was approved in 2014, and currently, 25 mg, 50 mg and 100 mg capsules of thalidomide are available. Because the blood half-life of thalidomide is only about 5 hours, it may be possible to control symptoms by administration of the drug every other day, as is also done with oral steroid therapy. Although there are no data on the efficacy of alternate-day thalidomide administration, such an administration schedule may be needed during the course of treatment. For example, when increasing the dose by 50 mg from 50 mg every day, an additional dose can be administered every other day (50 mg on the first day, 100 mg on the second day, 50 mg on the third day, etc.). For dose reduction, 50 mg daily dosing can be changed to 50 mg every other day dosing (50 mg every 2 days). When the attending physicians increase or decrease the dose of thalidomide on an alternate-day schedule, accurate records should be reported. The attending physicians should always give both oral and written instructions about dose increases or decreases to ensure correct management of thalidomide and not leave the judgement to the patients.

Administration of thalidomide every other day has also been performed in some patients with multiple myeloma, but there has been no report on its effectiveness or safety.

b. Administration of thalidomide to patients receiving oral steroid therapy for ENL: Usually, it is not necessary to use thalidomide together with oral steroids. After the diagnosis of ENL is made, administration of steroids will be started if thalidomide is unavailable. If thalidomide is acquired later, switch to thalidomide. Steroids are tapered gradually according to the usual tapering schedule. Even if ENL is controlled by thalidomide, steroids must be tapered gradually to avoid adrenocortical insufficiency caused by a rapid decrease of the dosage.

If exacerbation or relapse of the symptoms of ENL occurs during gradual tapering of the steroid, increase dose of thalidomide.
c. Administration of thalidomide in Japan: Few new cases of leprosy have been reported recently in Japan. Over the 5 years from 2005 to 2009, a total of 15 Japanese leprosy patients were treated with thalidomide for ENL according to the data from the Japanese Leprosy Association (Table 3). Although the data were compiled from multiple centers with different treatment policies, these data are recognized as treatment outcome of thalidomide for ENL in Japan.

The dose of thalidomide is ranged from 50 mg/day to 100 mg/day (Table 3). In Japanese patients, symptoms of ENL are reported to be well-controlled with a smaller dose of thalidomide compared to Western patients. The average treatment period was 2 years and 5 months, which means long-term administration was required. The effect of thalidomide was judged by attending physicians.

d. Maximum dose of thalidomide: The upper dosing limit for thalidomide is set at 300 mg/day in Europe and the US, but dose up to 400 mg/day is permitted when symptoms are poorly controlled. Accordingly, the upper limit for Japanese patients should be 300 mg/day, and dose up to 400 mg/day should be used for large foreign residents in Japan who are poorly controlled with low dose.

e. Antimicrobial therapy with thalidomide: Treatment of ENL is performed while continuing the patient’s antimicrobial therapy for leprosy. Because it is desirable to eliminate the causative bacteria as rapidly as possible in order to prevent further ENL. Also, if anti-leprosy drugs are discontinued, it is common for patients to refuse to resume treatment due to the psychological effect on the patients, which means they have misunderstanding that ENL is caused by taking anti-leprosy drugs.

f. Other drugs for ENL: If it is difficult to treat ENL with thalidomide for some reason, oral steroid therapy is available. Treatment of prednisolone should be started from 0.5 to 1 mg/kg/day. While it is recommended to start the dose of prednisolone at 1 to 2 mg/kg in Europe and the US, it is possible to control ENL in Japanese patients with initial dose of 0.5 to 1 mg/kg. Steroids are gradually tapered according to the usual tapering schedule of the drug, and it is better to extend the tapering period, especially after the daily dose is decreased to low level.

Systemic steroid therapy may be discontinued if the patient only has a small number of lesions of ENL. However, patients with high BI may develop recurrent

### Table 3  Details of Thalidomide use in Japan (2005-2009)

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Country</th>
<th>Classification</th>
<th>Concomitant drugs</th>
<th>Duration of THA</th>
<th>Max. dose of THA</th>
<th>Total dose of THA</th>
<th>Efficacy of THA</th>
<th>Side effects of THA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50s</td>
<td>M</td>
<td>Japan</td>
<td>BL/MB</td>
<td>CYA, PSL, CLF, AZP</td>
<td>4 mo</td>
<td>300 mg/d</td>
<td>8.3 g</td>
<td>no effect</td>
<td>Deep vein thrombosis, pulmonary embolism</td>
</tr>
<tr>
<td>2</td>
<td>40s</td>
<td>M</td>
<td>Philippines</td>
<td>LL/MB</td>
<td>PSL, CLF</td>
<td>7 mo</td>
<td>100 mg/d</td>
<td>approx. 5.8 g</td>
<td>effective</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>70s</td>
<td>M</td>
<td>Japan</td>
<td>LL/MB</td>
<td>PSL, CLF</td>
<td>2 yr 10 mo</td>
<td>100 mg/d</td>
<td>approx. 36 g</td>
<td>effective</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>20s</td>
<td>F</td>
<td>Philippines</td>
<td>LL/MB</td>
<td>PSLiv, PSL, CLF</td>
<td>1 yr 3 mo (continuing)</td>
<td>100 mg/d</td>
<td>approx. 15 g (continuing)</td>
<td>effective</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>60s</td>
<td>M</td>
<td>Japan</td>
<td>LL/MB</td>
<td>PSL, CLF</td>
<td>4 yr 9 mo</td>
<td>100 mg/d</td>
<td>approx. 43 g</td>
<td>slightly effective</td>
<td>not clear</td>
</tr>
<tr>
<td>6</td>
<td>30s</td>
<td>M</td>
<td>Brazil</td>
<td>LL/MB</td>
<td>PSL, CLF</td>
<td>10 mo</td>
<td>100 mg/d</td>
<td>13 g</td>
<td>effective</td>
<td>constipation</td>
</tr>
<tr>
<td>7</td>
<td>70s</td>
<td>M</td>
<td>Japan</td>
<td>LL/MB</td>
<td>CLF</td>
<td>4 mo</td>
<td>50 mg/d</td>
<td>4.6 g</td>
<td>effective</td>
<td>none</td>
</tr>
<tr>
<td>8</td>
<td>80s</td>
<td>M</td>
<td>Japan</td>
<td>LL/MB</td>
<td>no</td>
<td>5 mo</td>
<td>100 mg/d</td>
<td>11.2 g</td>
<td>effective</td>
<td>none</td>
</tr>
<tr>
<td>9</td>
<td>70s</td>
<td>M</td>
<td>Japan</td>
<td>LL/MB</td>
<td>PSL, CLF</td>
<td>6 yr 8 mo</td>
<td>100 mg/d</td>
<td>approx. 95 g</td>
<td>effective</td>
<td>none</td>
</tr>
<tr>
<td>10</td>
<td>70s</td>
<td>M</td>
<td>Japan</td>
<td>BL-LL/MB</td>
<td>no</td>
<td>5 yr 6 mo</td>
<td>100 mg/d</td>
<td>approx. 85.5 g</td>
<td>effective</td>
<td>none</td>
</tr>
<tr>
<td>11</td>
<td>70s</td>
<td>F</td>
<td>Japan</td>
<td>BL-LL/MB</td>
<td>no</td>
<td>1 yr 7 mo</td>
<td>50 mg/d</td>
<td>approx. 1.5 g</td>
<td>not clear</td>
<td>none</td>
</tr>
<tr>
<td>12</td>
<td>80s</td>
<td>M</td>
<td>Japan</td>
<td>BL-LL/MB</td>
<td>no</td>
<td>2 yr 9 mo</td>
<td>75 mg/d</td>
<td>approx. 3.25 g</td>
<td>effective</td>
<td>none</td>
</tr>
<tr>
<td>13</td>
<td>50s</td>
<td>M</td>
<td>Japan</td>
<td>LL/MB</td>
<td>PSL, CLF, NSAIDs</td>
<td>3 yr 6 mo</td>
<td>100 mg/d</td>
<td>approx. 3.5 g</td>
<td>effective</td>
<td>none</td>
</tr>
<tr>
<td>14</td>
<td>80s</td>
<td>M</td>
<td>Japan</td>
<td>BL-LL/MB</td>
<td>no</td>
<td>5 yr</td>
<td>50 mg/d</td>
<td>approx. 101.4 g</td>
<td>effective</td>
<td>none</td>
</tr>
<tr>
<td>15</td>
<td>70s</td>
<td>M</td>
<td>Japan</td>
<td>LL/MB</td>
<td>CLF, NSAIDs</td>
<td>1 yr</td>
<td>100 mg/d</td>
<td>approx. 46.6 g</td>
<td>effective</td>
<td>none</td>
</tr>
</tbody>
</table>

Includes new cases and relapsed cases.
ENL over time, making it difficult to withdraw steroids completely.

g. Treatment of ocular symptoms: The effectiveness of thalidomide alone for treatment of iridocyclitis and scleritis is unknown. Therefore, it is necessary to use thalidomide and topical steroids (eye drops) in combination. If these symptoms cannot be controlled by combination of thalidomide and steroids (eye drops), add subconjunctival steroid injection or systemic steroid administration. Management of the pupil and intraocular pressure must also be performed.

h. Mental health: Treating ENL requires long-term use of thalidomide with careful guidance. Also, various side effects of steroid therapy can develop with long-term administration, and ENL itself causes pain, fever, blindness, and other symptoms. Therefore, it is important to support patients for their mental health (counseling and antidepressants, etc.).

4. Clofazimine

Clofazimine (CLF, B663 (Lamprene®, Sandoz Chemical)) is part of the WHO multidrug therapy (MDT) regimen, which is standard treatment for leprosy with rifampicin (RFP) and dapsone (DDS). When MDT is performed, CLF is taken at 300 mg once every 28 days and at 50 mg/day for the other 27 days. A common side effect of CLF is reddish brownish skin pigmentation, and skin eruptions tend to become blackish brown. Dry skin is another well-known side effect. It is thought that accumulation of CLF in macrophages is gradually effective for ENL by an anti-inflammatory effect.

CLF suppresses the symptoms of ENL, especially iridocyclitis. Therefore, CLF may be administered at the occurrence of ENL or when ENL is suspected from symptoms such as neuralgia (Table 3). However, it does not have an obvious anti-ENL action, unlike steroids or thalidomide. Usually, we try to reduce the daily steroid dose or the dose of thalidomide by using CLF in the dose range from 50 mg to 100 mg/day (up to 200 mg/day in other countries). However, pigmentation becomes conspicuous when CLF is administered at 100 mg/day, and diarrhea or abdominal pain can also occur, so patients often dislike this medication.

5. Other treatments for ENL

It may be possible to treat ENL with medications and biologic agents that inhibit TNF-α production, as well as immunosuppressive drugs like cyclosporin²⁵-²⁷.

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**Table 4 Side Effects of Thalidomide**

<table>
<thead>
<tr>
<th>Serious side effects</th>
<th>Main side effects (Phase II clinical trial in Japan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Teratogenicity (thalidomide embryopathy)</td>
<td>1. Constipation</td>
</tr>
<tr>
<td>2. Deep vein thrombosis, Pulmonary embolism</td>
<td>2. Drowsiness</td>
</tr>
<tr>
<td>3. Cerebral infarction</td>
<td>3. Neutropenia</td>
</tr>
<tr>
<td>4. Peripheral neuropathy (numbness of limbs, tingling, pain, burning sensation, etc.)</td>
<td>4. Numbness</td>
</tr>
<tr>
<td>5. Myelosuppression (neutropenia, leukopenia, erythropenia, thrombocytopenia, etc.)</td>
<td>5. Dry mouth</td>
</tr>
<tr>
<td>6. Infectious diseases (serious infections such as pneumonia)</td>
<td>6. Leukocytopenia</td>
</tr>
<tr>
<td>7. Interstitial pneumonia</td>
<td>7. Skin rash/eruption</td>
</tr>
<tr>
<td>10. Oculomucocutaneous syndrome (Stevens-Johnson syndrome), Toxic epidermal necrolysis (TEN)</td>
<td>10.</td>
</tr>
<tr>
<td>11. Lethargy, somnolence, sedation</td>
<td>11.</td>
</tr>
<tr>
<td>14. Cardiac disorders (arrhythmia, bradycardia, etc.)</td>
<td>14.</td>
</tr>
<tr>
<td>15. Hypothyroidism</td>
<td>15.</td>
</tr>
<tr>
<td>16. Tumor lysis syndrome</td>
<td>16.</td>
</tr>
<tr>
<td>17. Hepatic dysfunction</td>
<td>17.</td>
</tr>
</tbody>
</table>

6) Side effects of thalidomide

Significant side effects of thalidomide include teratogenicity, deep vein thrombosis, pulmonary embolism, cerebral infarction, peripheral neuropathy (PN), myelosuppression, infectious diseases, interstitial pneumonia, gastrointestinal perforation, ischemic heart disease, oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (TEN), lethargy, somnolence, sedation, convulsion, orthostatic hypotension, cardiac disorders, hypothyroidism, tumor lysis syndrome and hepatic dysfunction. In phase II clinical trials performed in Japanese patients with relapsed/refractory multiple myeloma, sleepiness, constipation, dry mouth, numbness, neutropenia, and leukopenia were recognized as major side effects (Table 4)²⁸. If these side effects develop, it is necessary to stop/decrease administration or take other appropriate countermeasures. It is reported that PN was relieved by
vitamin B₆.²⁹

7) In conclusion
Thalidomide is an effective drug for ENL, but it can have serious side effects. The physicians who prescribe thalidomide to improve the symptoms of ENL need to have sufficient knowledge and the correct information of this medicine and to continue the appropriate use of thalidomide. We are awaiting the development of safer and more effective drugs.

References


Message from thalidomide victims

We were born with disabilities caused by thalidomide disaster and live with various difficulties in our daily lives. If this medicine did not exist, we would not have suffered damage, so we do not want such a horrible medicine to be used again.

However, if someone can be saved by thalidomide, we hope that it will be used without errors. The medicine itself is not responsible for the tragedy, but those who use it not knowing what happened in the past and without sufficient knowledge will be supposed to take responsibility for it. We do not want to see any more of the scene that drug company representatives and government officials just bow their heads to apologize for a drug disaster repeated. In order not to repeat the same mistakes, we want as many people as possible to be concerned. We would like these disasters to be taught as part of compulsory education so everyone can be aware that “It could happen to you, too”.

If thalidomide is used, its use should be restricted under strict rules. “Everyone involved with this medicine, medical institutions, doctors, pharmacists, patients who need thalidomide, and their family members, please make a correct decision”. If the rules are not observed, it will not be able to prevent recurrence of the case unless its use is completely prohibited. Our experience of such tragedy is quite enough on our own.

Hoping that any more damage by thalidomide will not occur, we will continue to watch for the proper use of thalidomide.

The Ishizuea Foundation (Thalidomide Welfare Center)