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The role of thalidomide in the management of erythema nodosum leprosum

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Summary Erythema nodosum leprosum (ENL, Type 2 reactions) complicates lepromatous and borderline lepromatous leprosy and can affect many organ systems, often with irreversible damage. The reactions commonly occur in the 2 years after starting treatment and often run a recurrent or chronic course, sometimes for many years. Even with WHO multi-drug therapy about 30% of LL patients experience ENL.

We review drug management of ENL focussing on data from controlled trials and other studies. The treatment of ENL is difficult because high doses of steroids may be required for prolonged periods and do not always control the inflammation. The paradox of ENL is that it can be a life-threatening disorder and requires control with immunosuppression which may itself pose life-threatening risks for patients. Treatment with thalidomide provides an effective alternative to steroid therapy, gives better long-term control and avoids the adverse effects of prolonged steroid therapy.

Controlled clinical trials have demonstrated that thalidomide rapidly controls ENL and is superior to aspirin and pentoxifylline. However, thalidomide is teratogenic when taken in early pregnancy and is unavailable in many leprosy endemic countries. We discuss the role of thalidomide in treating ENL, the complications encountered and risk reduction strategies that can be used. These include good patient selection and counselling, close supervision and adequate access to appropriate contraception.

Further research is needed to improve the understanding and treatment of this severe and debilitating complication of leprosy. Topics for research include:

i. The development of validated tools to measure the severity and/or activity of ENL.
ii. A detailed assessment of the neurotoxic effects of thalidomide when used to treat ENL.
iii. A well designed trial comparing thalidomide with prednisolone.
iv. The development of a safe and effective alternative to both steroids and thalidomide.

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Search Strategy

Papers for this review were identified by repeated searches of PubMed with various combinations of the following search terms: 'leprosy', 'erythema nodosum leprosum', 'type 2 reactions', 'steroids', 'corticosteroids', 'lepra', 'Hansen*'.

Searches of LILACS using the terms 'eritema nodoso hansenico' and 'erythema nodosum leprosum' were also conducted.

References from the articles retrieved from the searches were also used.

All searches were complete to the end of July 2007.

Erythema Nodosum Leprosum and Complications

ENL is an immune mediated reactional state which commonly complicates lepromatous leprosy (LL) and less frequently borderline lepromatous (BL) leprosy. It is characterised by the presence of cutaneous nodules but other organ involvement and systemic upset may occur.[1] The condition is termed ENL regardless of the site of involvement. Jopling proposed the term type 2 reaction to distinguish it from type 1 (reversal) reactions.[2] The skin lesions usually occur in crops as painful and tender erythematous papules or nodules. They develop over a few hours, last for several days and then slowly subside often leaving some dark staining of the skin.[1] Lesions may also be pustular or bullous.[3,4] Deeper lesions in more severe episodes cause a panniculitis. In BL leprosy, ENL papules may develop in the sites of existing BL lesions. Fever and malaise frequently accompany the skin lesions; in severe episodes there may be hypotension and tachycardia which may mimic septic shock and severe ENL can be life-threatening. ENL may also produce iridocyclitis, neuritis, arthritis, dactylitis, lympadenitis, orchitis and nephritis.[1] Nerves are often tender and enlarged but usually the neuritis is less dramatic than that associated with type 1 reactions. However, loss of nerve function may occur rapidly.[1]

The Operational Guidelines of the Global Strategy for Further Reducing the Leprosy Burden published by WHO in 2006 describes ENL as a syndrome of 'complex medical problems requiring careful management by experienced clinicians'.[5]

There are no prospective clinical studies on the clinical features of ENL and no good data on the frequency of particular features, duration or severity of ENL. In a retrospective study in India Pocaterra *et al.* found that the mean time to presentation with ENL was 3.7 months after starting multi-drug therapy (MDT).[6] However, patients may present with ENL as their first manifestation of leprosy. ENL may continue for many years and we have had patients at The Hospital for Tropical Diseases in London who have continued to have ENL for 7 years or more. ENL may also occur after completion of MDT.

Three patterns of ENL were identified in a cohort of 82 Indian patients with ENL; single acute episodes, recurrent acute episodes and chronic ENL.[6] Acute single episodes were defined as a single episode responding to steroid treatment and accounted for only 6% of episodes, acute multiple ENL comprised recurrent episodes with periods off all treatment, and chronic when patients needed steroid treatment for more than 6 months. The acute multiple and chronic types accounted for 32% and 62% of the case types respectively. Murata recognised that the condition 'may be acute, subacute, or chronic' in the 1912 description in which the term ENL was first suggested.[7]

ENL is debilitating and adversely affects the morale of even the most optimistic.

Recurrent skin lesions may result in scarring and inflammation of subcutaneous tissue may cause fixation and reduce mobility in joints.[1] In the eyes chronic iridocyclitis leads to synechiae formation, glaucoma and blindness.[8] The neuritis associated with ENL may result in permanent nerve function impairment. The orchitis results in testicular atrophy which if bilateral may result in hypogonadism and sterility. Men with leprosy are at increased risk of osteoporosis and this is associated with hypogonadism.[9] The possible association of osteoporosis with ENL and corticosteroid therapy has not been investigated. Secondary amyloidosis may occur if the reaction is inadequately controlled.

There is no validated scale for assessing severity of ENL. However, various authors have defined mild disease as the presence of less than 10 skin lesions with no systemic symptoms. Moderate disease can be defined as that present when multiple skin lesions are present and severe when lesions are pustular or ulcerating and/or there is other organ system involvement.[10]

In the Indian study the typical patient with ENL was a male aged 34.7 years who experienced chronic ENL over a 2-year period.[6] These patients are likely to be family wage earners so ENL also has serious economic and social consequences which have not been documented.

Epidemiology and Risk factors

The published data suggests that LL and BL patients still have high rates of ENL even those taking WHO MDT. The most appropriate data sets are those that report on the BL and LL subgroups of the MB category since it is these patients who are at risk of developing ENL. There is wide geographical variation in the prevalence of ENL with high rates in Asia and Brazil and probably lower rates in Africa although there is little data from Africa. A retrospective study of clinic-based Indian patients 1990–2000 found a rate of almost 50% in those with LL and 9% in BL cases[6] and another retrospective hospital study from Nepal of 649 cases of BL leprosy and LL between 1989 and 1997 reported an ENL rate of 33% in LL cases and 11% in BL cases.[11] A study from Brazil of reactional episodes during a 24-month period of MB MDT found that 31% of individuals experienced ENL.[12] Two prospective studies from Thailand found overall rates of 37% and 12%.[13,14] ENL rates are much lower when coming from field studies of MB patients as in the Ethiopian AMFES Study which reported 5·3%.[15] Rates are also likely to be lower when patients are diagnosed earlier and when they are only followed for a year during MDT. Both the Nepali and Indian studies found that LL disease and a bacterial index (BI) greater than 4 at diagnosis were risk factors for ENL. In the latter study LL patients were 8·4 times more likely to develop ENL than those with BL disease. Individuals with BL leprosy with a BI of 4 or more were 5·2 times more likely to have ENL than BL patients with a BI of less than 4.

Pathophysiology

The principal pathology underlying ENL is antigen-antibody complex formation and deposition in tissues. This results in local activation of complement and development of local inflammation with neutrophil polymorph migration to the lesions. Direct immunofluorescence studies have demonstrated granular deposits of immunoglobulin and complement in

the dermis in most ENL lesions but not in those of uncomplicated LL disease.[16] Other workers have also demonstrated the presence of immune complexes in cutaneous ENL lesions.[17,18]

Tissue oedema and fibrinoid necrosis in vessels may also be present. ENL lesions classically show an intense perivascular infiltrate of neutrophils throughout the dermis and subcutis.[19]

There is T lymphocyte and macrophage activation and expression of mRNA for tumour necrosis factor (TNF) and interleukin (IL)-12 in the skin.[20] High levels of circulating TNF have been found in the serum of some individuals with ENL.[21,22] In the Brazilian study not all patients had high levels of TNF and clinical improvement was not necessarily related to TNF levels. TNF levels in individuals in Nepal with milder ENL reactions have been found to be low.[23] *In vitro* peripheral blood mononuclear cells from individuals with ENL secrete increased amounts of TNF following stimulation by *M. leprae* or *M. leprae* antigens compared to individuals with other forms of leprosy.[24,25] There is no single diagnostic test which confirms the diagnosis of ENL.

Management of ENL

Individuals should continue taking MB MDT and those presenting with ENL should be commenced on MDT as well as specific treatment for ENL. Analgesics and antipyretic agents can be used for milder disease.

ENL may also be triggered by intercurrent infections and psychological stress. A wide differential diagnosis should be remembered in individuals in whom ENL is relapsing or not responding to treatment.

CORTICOSTEROIDS

The use of adrenocorticotrophic hormone in the management of ENL was first reported by Roche *et al.* in 1951[26] and corticosteroids remain the mainstay of treatment for ENL but they are often required for prolonged periods at high doses.[6] The treatment of more severe reactions is often started at a dose of prednisolone 60 mg daily and pulsed steroid therapy in recurrent disease has been reported in two small studies.[27,28] The Indian study by Pocaterra *et al.* shows how poor the control given by corticosteroids is in patients with chronic ENL (Figure 1.) with individuals needing repeated high does of steroids and taking an average of 421 mg of prednisolone per month.

Individuals with chronic recurrent ENL extending over many years are at risk of developing complications secondary to prolonged corticosteroid therapy and may require alternative treatments. Sugumaran described the adverse effects of steroid therapy in 249 patients with ENL. This study was uncontrolled but reported higher rates of cataract, diabetes and tuberculosis in the ENL group compared to a group of patients receiving steroids for type 1 reactions.[29] A fatal case of *Strongyloides stercoralis* hyperinfection following steroid treatment of ENL has also been reported.[30]

There are no data from controlled studies regarding the treatment of neuritis or iridocyclitis associated with ENL.

The ILEP Technical Bulletin on the management of ENL recommends treating severe ENL with corticosteroids at a starting dose of 30–60 mg and reducing every week by

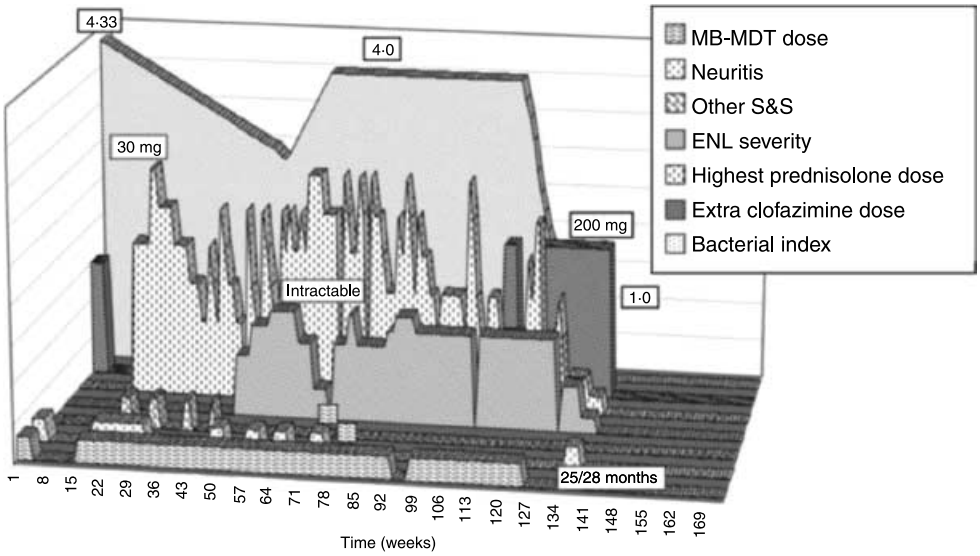

Figure 1. Clinical indices in a chronic case of ENL. Reproduced from Pocaterra L, Jain S, Reddy R et al. Clinical course of erythema nodosum leprosum: an 11-year cohort study in Hyderabad, India. Am J Trop Med Hyg. 2006 May; 74(5):868-79. MB-MDT = Multidrug therapy for multibacillary disease, S&S = Symptoms and signs, BI = Bacterial index.

5–10 mg. It notes that a maintenance dose of 5–10 mg may be needed for several weeks to prevent recurrence of ENL.[10]

The 1998 WHO Expert Committee on Leprosy report discussed the management of type 1 (reversal) reactions and ENL together[31] advising that 'severe ENL can be treated with prednisolone, as for reversal reaction' (a 12-week course of prednisolone). This overlooks the chronic, recurrent nature of ENL and is not supported by any data. We agree with the recent WHO Global Strategy statement that patients with ENL should be managed by staff with experience of the condition. However, the document lacks specific guidance and states that 'Short courses of steroids are often used, but other drugs are also useful.'[5] For those individuals with clinically significant ENL a short course of steroids will rarely give adequate control of the ENL.

CLOFAZIMINE

Treatment with clofazimine improves ENL and is a mild anti-inflammatory.[32] However, clofazimine therapy does not control severe ENL and takes 4 to 6 weeks to become active. The daily dose of 50 mg in MB MDT probably protects at-risk individuals from ENL. This has never been formally tested but a multi-centre study of different chemotherapy regimes in patients with lepromatous leprosy showed that regimes containing clofazimine given 100 mg three times a week for 5 years were associated with a lower rate of ENL.[33] The protective effect of clofazimine in preventing ENL is lost after 1 year when MB MDT is stopped. This beneficial effect will be shortened further if uniform MDT is introduced.

The dose of clofazimine can be increased to 300 mg daily in those with ENL, but may worsen clofazimine pigmentation and increase the risk of clofazimine crystal enteropathy.[34,35]

The WHO Expert Committee recommended that the drug should not be maintained at this dose (300 mg daily) for more than a year.[31]

THALIDOMIDE

Thalidomide was first developed in 1954 and subsequently marketed in Europe, Australia and Canada as a sedative and anti-emetic. The drug was not approved in the USA by the Food and Drug Administration because of concerns about safety and neurotoxicity.

Reports of limb and other congenital abnormalities in the children of women who had taken thalidomide during pregnancy led to the drug being withdrawn from European markets in 1961. About 10,000 children have abnormalities attributed to intrauterine exposure to thalidomide.

Thalidomide is a racemic glutamic acid analogue composed of two enantiomers R- and S-thalidomide (stereoisomers that are mirror images of one another) which interconvert under physiological conditions. The two enantiomers have differing properties; one is a more potent suppressor of TNF release by stimulated peripheral blood mononuclear cells whilst the other is sedative.[36] Thalidomide undergoes hydrolysis at pH 7 in aqueous solution and this degradation leads to the formation of more than 20 products which are responsible for the activity. The exact mechanisms of action of these products is not clear but TNF, interferon-γ, interleukins 10 and 12, cycloxygenase 2 and possibly the pro-inflammatory transcription factor nuclear factor κ B (NF-κB) are all affected.[37] Thalidomide has effects on angiogenesis, immune function and inflammation. *In vitro* work has demonstrated that *M. leprae* induced activation of NF-κB in a Schwann cell line leading to transcription repression mediated by TNF is inhibited by thalidomide.[38]

In 1965 Sheskin reported the effectiveness of thalidomide in the management of ENL.[39] Thalidomide is used to treat dermatological conditions such as lupus erythematosus, nodular prurigo, aphthous ulceration and Beçhet's syndrome when they are refractory to other treatments.[40] Thalidomide is effective in the management of myeloma.[41]

THALIDOMIDE AND ENL

The effectiveness of thalidomide in ENL is primarily due to its action on TNF but other mechanisms may contribute to its anti-inflammatory effect.

Eight Brazilian patients, who had ENL with systemic symptoms and elevated serum TNF, when treated with thalidomide had an associated reduction in the TNF levels. Recurrence of the ENL after cessation of thalidomide was again associated with an elevation in serum TNF levels.[42]

Treatment with thalidomide in the study of mild ENL from Nepal although resulting in clinical improvement was associated with an unexpected rise in plasma TNF levels and increased expression of IL-2 by CD4 and CD8 + cells at day 7.[23] In this group TNF levels were lower than in control patients and the authors postulate that TNF levels are elevated in individuals with more severe ENL with systemic manifestations. Thalidomide treatment was associated with a reduction in plasma soluble 1L-2 receptor, a marker of inflammation but the mechanism of this is unclear.

In two patients with successfully treated ENL thalidomide therapy was associated with a reduction in the numbers of circulating CD4 + lymphocytes.[43]

Thalidomide-associated increases in TNF have been reported in other disease states such as HIV related oral aphthous ulceration.[44] Thalidomide was associated with a good clinical response. However a randomised controlled trial of thalidomide in life-threatening toxic epidermal necrolysis (a TNF mediated condition) was ended early because of an excess mortality in the thalidomide arm of the study which was associated with higher plasma concentrations of TNF.[45]

Table 1 shows prospective controlled trials of thalidomide in ENL. Only two studies have been completed since the introduction of MDT.[46,47]

The double blind randomised study of 22 patients by Villahermosa *et al.*[47] compared thalidomide 100 mg daily with 300 mg daily given for 1 week. The lower dose group then received 50 mg daily for 2 weeks followed by dummy capsules for 4 weeks. The group that initially received 300 mg of thalidomide was weaned down to zero over the following 6 weeks. There was no significant difference in the response of the two groups at the end of the first week of treatment with thalidomide. The lower dose group however experienced a statistically significant flaring of skin lesions during the 7-week treatment period. Global assessment scores of symptom severity improved on thalidomide. The three individuals deemed to be treatment failures were all in the higher dosage arm of the study.

Sales *et al.* recruited 44 Brazilian patients with ENL into a double blind randomised controlled trial comparing pentoxifylline and thalidomide.[46] Individuals with neuritis were excluded and follow-up was short at 30 days. Thalidomide was more effective than pentoxifylline but one can not be confident that ENL severity was similar in the two groups.

The open trial by Iyer and Ramu[48] used thalidomide 300 mg daily in 36 controls for 8 weeks and then maintained them on 50 mg daily for up to 1 year whilst studying the effect of clofazimine 300 mg in ENL. The onset of action was more rapid with thalidomide but the effect was not sustained as well as with clofazimine possibly because of the relatively low dose of thalidomide used for maintenance.

Iyer *et al.* published a double blind trial comparing thalidomide 400 mg daily with aspirin in 92 patients treated for 7 days.[49] Thalidomide was faster and more efficacious in reducing fever and the number of skin lesions. The effect on nerve and eye involvement was 'less pronounced' but still deemed to be superior to that of aspirin.

A double blind study of 10 corticosteroid-dependent Malaysian patients demonstrated that thalidomide 300 mg daily was superior to placebo in reducing steroid requirement.[50] The same centre also examined the effect of thalidomide 300 mg in individuals with moderately severe ENL i.e. those not requiring continual corticosteroids. The severity of ENL was less during therapy with thalidomide than it was during administration of the placebo.[51]

Sheskin and Convit's double blind study in 59 Venezuelans, over a quarter of whom were women, demonstrated that thalidomide 400 mg daily was associated with a statistically significant improvement when compared to placebo.[52] An earlier single blind study by Sheskin[53] used thalidomide 400 mg followed by placebo in a subsequent reaction. The thalidomide was more effective than the placebo in all 13 patients studied.

The effect of thalidomide on non-cutaneous clinical and laboratory parameters is commented on to varying degrees in these studies. An improvement in neuritis is reported in three but without documenting how this was assessed.[47,48,52]

There have been numerous open uncontrolled studies reporting the effectiveness of thalidomide in the management of ENL. The studies of both types whether controlled or not often report the rapidity of onset of the effect of thalidomide in controlling symptoms.

Table 1. Prospective studies using thalidomide in type 2 reactions

Author Year Country	Type of study	Entry criteria	Total number enrolled (number of women)	Intervention	Outcome measures	None cutaneous effects of thalidomide assessed in study	Conclusion
Sales[46] 2007 Brazil	Randomised, controlled double blind	ENL without neuritis	44 (6)	Thalidomide 300 mg/day or pentoxifylline 1·2 g/day	Partial or total improvement	Yes	Thalidomide superior to pentoxifylline.
Villahermosa[47] 2005 Phillipines	Randomised, controlled double blind	Biopsy confirmed ENL. ≧ 10 lesions	22 (0)	Thalidomide 100 mg/day or 300 mg/day for one week then tapered to zero.	%age change in number of lesions	Yes	No difference in speed of onset of improvement. Improvement sustained in higher dosage group.
Iyer[48] 1976 India	Randomised controlled	Recurrent 'reactive episodes' lepromatous patients	72 (0)	Clofazimine 300 mg or thalidomide 300 mg for 8 weeks	Time taken for control of reactions	No	Improvement maintained more by clofazimine treated group.
Iyer[49] 1971 India, Mali, Somalia, Spain	Double blind	ENL, neuritis or nerve function impairment	92 (not stated)	Thalidomide 400 mg or aspirin 1600 mg daily	Improvement in clinical signs	Yes	Thalidomide superior in managing skin lesions, fever, nerve and eyes and testes, lymph nodes liver and spleen.
Waters[50] 1971 Malaysia	Double blind, placebo controlled	Steroid dependent biopsy proven ENL	10 (0)	Thalidomide 300 mg daily or placebo	Steroid requirement	No	Steroid requirement reduced during thalidomide treatment period.
Pearson[51] 1969 Malaysia	Double blind, placebo controlled	ENL	12 (1)	Thalidomide 300 mg daily or placebo	Clinical, laboratory and additional therapy required	Yes	Severity of ENL less during thalidomide treatment

Table 1. *continued*

Author Year Country	Type of study	Entry criteria	Total number enrolled (number of women)	Intervention	Outcome measures	None cutaneous effects of thalidomide assessed in study	Conclusion
Sheskin[52] 1969 Venezuela	Double blind, placebo controlled	Lepromatous leprosy with manifestations of 'lepra' reaction	52 (15)	Thalidomide 400 mg daily or placebo	Improvement	Yes	Thalidomide statistically significant difference compared to placebo
Sheskin[53] 1965 Israel	Placebo	Lepra reactions of lepromatous leprosy patients	13 (3)	Thalidomide varying doses	Improvement within 48 hours	No	Therapies containing thalidomide brought about clinical improvement, whereas placebo did not

Thalidomide was approved by the FDA in the USA in 1998 'in the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrences.'[54] Thalidomide may be prescribed on a named patient basis in the UK although the European Medicines Agency declined to licence it for ENL. The Australian Drug Evaluation Committee approved the use of thalidomide in myeloma and 'cutaneous manifestations of moderate to severe erythema nodosum leprosum'. The drug is manufactured and available in India and Brazil.[55] Brazilian law forbids the sale of thalidomide by commercial pharmacies and the amount dispensed is restricted. Physician and patient must sign a declaration that adequate counseling has been provided.[56]

The WHO Expert Committee advises that thalidomide should only be given to men or post-menopausal women who are dependent on corticosteroids.[31] The ILEP Technical Bulletin acknowledges the effectiveness of thalidomide and states that 'It has fewer adverse effects than corticosteroids'. However, it goes on to say that 'women of child-bearing age should never be given thalidomide'.[10]

Thalidomide is a good choice in men or post-menopausal women with difficult to manage ENL. Women of childbearing age should also not be denied an effective and sometimes life-saving drug provided that they and their physicians understand the risks associated with taking thalidomide.

Physicians must undertake a detailed assessment of the risks as well as the benefits before prescribing thalidomide. The patient and their partner should be educated about the drug and the adverse effects associated with it.

Drowsiness is a problem for many people taking thalidomide. Taking the drug in the evening can reduce the impact of drowsiness on daytime activities or dividing the dose may help some individuals.

Neuropathy is one of the adverse factors that limits the use of thalidomide. Patients taking thalidomide should be advised to report any new symptoms or worsening of pre-existing ones. This can be difficult as many individuals with ENL will have some nerve damage but it should not be assumed that deterioration in nerve function is due to ENL.

They should be allowed sufficient time to come to a decision. This may require more than one meeting with the prescribing physician so that questions can be answered and important points reiterated. It is important to emphasise to patients that they must not share their thalidomide tablets with anyone else.

The informed consent obtained when an individual decides to take the drug should form the basis of a contract.

The possibility of pregnancy should be excluded in women who are fertile. They should then be advised to use two forms of contraception. All patients should be seen on a monthly basis and women should have a pregnancy test performed at each visit. In the early phase of thalidomide therapy more frequent clinic attendances may be required.

The FDA when it approved the use of thalidomide introduced the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) programme. This is a mandatory registry and includes authorised patients, prescribers and pharmacies. The registered prescriber must contact the S.T.E.P.S programme and answer questions concerning the prescription of thalidomide including the dose. The patient must also contact the programme and answer a set of questions designed to ensure safe use of the drug. Once both the prescriber and patient have done this successfully the prescription is authorised. Finally a registered pharmacist

calls the programme to see if the prescription for thalidomide has been authorised and can be dispensed. A similar procedure must be followed in Europe and Australia.

The S.T.E.P.S programme in the USA appears to work well. Six thousand female patients at risk of pregnancy entered the programme up to the end of 2004. They were taking thalidomide for conditions including myeloma, other neoplasia, rheumatological and dermatological diseases. Only 0·2% were taking thalidomide for the management of ENL. There were three pregnancies, two of which were identified as a result of the programme before thalidomide was prescribed. The third case, a 44-year old woman with melanoma had had a negative pregnancy test on day eight of her menstrual cycle before starting thalidomide and two more negative tests during the first month of treatment. On day 35 she had a positive test and thalidomide was stopped. The test result was confirmed the following day and a week later. Four weeks after the first positive test she had a spontaneous abortion.[57]

Pregnancy prevention programmes require good healthcare infrastructure, time and finance. These things are often not readily available in leprosy-endemic countries.

Only one month's supply of thalidomide should be prescribed to ensure that regular assessments and pregnancy tests are negative before further drugs are dispensed.

In severe ENL we suggest starting with thalidomide at a dose of 400 mg nocte to control the main symptoms. This should be reduced to 300 mg daily as soon as possible, usually within a week. The thalidomide is then reduced more slowly by 100 mg each month. During this period the patient should be assessed to ensure the ENL has not deteriorated. Any deterioration should be treated by increasing the thalidomide again for a few weeks. The patient should be stabilised on the lowest dose of thalidomide that controls the disease and continue at this dose for a period of 2-3 months.

A patient already on steroids may have ENL that is more difficult to control. In the experience of one of the authors, controlling ENL by replacing steroids with thalidomide is much more difficult than when using thalidomide from the beginning. It may take several weeks to reduce the steroids and obtain control with thalidomide alone. This is a further argument for switching to thalidomide early although in many settings steroids will be used first. The steroids should be reduced gradually aiming for control of ENL with thalidomide alone within 6 weeks. A further indication for switching to thalidomide would be any suggestion of early amyloidosis, especially persistent mild albuminuria, despite treatment with steroids.

WHO has issued conflicting statements with respect to the use of thalidomide. The drug is acknowledged as an effective treatment for ENL by the WHO Expert Committee on Leprosy[31] but other publications state that WHO does not support the use of thalidomide in ENL[58] or even more emphatically that there is no role for thalidomide in the management of leprosy.[59] Dr Pannikar, Communicable Diseases (Leprosy Group) WHO, published an article stating that ENL reactions are '. . .rare. . .(mostly) mild in nature. . .and do not require any specific treatment except with some analgesics/antipyretics.'[60] This view does not concur with the published evidence on the importance of ENL, albeit to small numbers of patients and provoked a vigorous response from leprosy workers[61–63] around the world arguing for the place of thalidomide in the management of ENL.

There are little good data concerning the effect of thalidomide on the neural and ocular manifestations of ENL which are disabling and occur commonly.[1] There are case series suggesting that thalidomide may be effective in treating neuritis[64] and iritis,[65] which are usually managed with corticosteroids.

Adverse effects of thalidomide

TERATOGENICITY

Thalidomide causes a wide range of abnormalities and almost any organ system may be affected.[66] The most characteristic abnormality is limb reduction with the upper limbs being more frequently affected than the lower limbs. The ears and eyes are the second most frequently affected group after the limbs.

The teratogenic effect of thalidomide occurs when it is taken between days 20 and 36 after conception. Thalidomide appears to intercalate into guanine rich promoter sequences of insulin growth factor-1 (IGF-1) and fibroblast growth factor (FGF) genes.[67] IGF-1 and FGF act in combination to stimulate limb initiation and thalidomide has been shown to suppress guanine rich promoter sequences in myeloma cells.[68]

Even if the teratogenic enantiomer in humans could be determined and separate R- and S-thalidomides produced, because each readily reverts to a racemic mixture under physiological conditions the possibility of teratogenic fetal damage would remain.[36]

The drug is present in human semen after ingestion[69] but there are no reports of teratogenicity caused through exposure to semen of men who are taking thalidomide, but it has occurred in experiments with rabbits via this route.[70]

NEUROPATHY

A prospective study of 135 patients with dermatological conditions treated with thalidomide demonstrated that a peripheral neuropathy occurred in 20% of individuals during the first year of treatment.[71] The neuropathy manifests as painful paraesthesia and/or numbness. The feet are affected before the hands in a glove-stocking type distribution. Weakness may also occur. The neuropathy correlates with the daily dose administered and is permanent in 50%. It may progress for some time after cessation of the drug[72] and any improvement that does occur may do so slowly.

Nerve conduction studies show a predominantly sensory, axonal, length-dependent neuropathy. Nerves show loss of large myelinated fibres and little inflammation when examined histologically.[72] Reduction of sensory nerve action potential amplitude and relative conservation of nerve conduction velocities were the electrophysiological features of thalidomide neuropathy in 13 individuals without leprosy who were taking thalidomide for severe dermatological conditions.[73] There are no data concerning neuropathy attributable to thalidomide in individuals with ENL.

THROMBOEMBOLISM

Thalidomide when used as monotherapy in myeloma is associated with thromboembolism in 3% of patients.[74] The rate increases to 14% when thalidomide is combined with dexamethasone. A single case of iliac deep vein thrombosis has been reported in a woman with ENL treated with a combination of thalidomide, prednisolone, dexamethasone and cyclophosphamide.[75]

CUTANEOUS

Adverse effects on the skin have been reported to occur in 3% of myeloma patients receiving thalidomide.[74] Rarer severe cutaneous adverse reactions such as erythema multiforme, erythroderma and toxic epidermal necrolysis have been attributed to thalidomide.[40]

OTHER ADVERSE EFFECTS

Thalidomide frequently causes somnolence and constipation which may limit the usefulness of the drug. The degree of somnolence is severe in up to 11% of patients.[74] Other adverse effects which may lead to discontinuation of thalidomide include dizziness, nausea, peripheral oedema, neutropenia and amenorrhoea. Hypothyroidism has been reported following the administration of thalidomide.[76]

Other Drugs

Pentoxifylline

This methylxanthine derivative used is in the management of peripheral vascular disease. It has been shown to inhibit the production of TNF both *in vitro* and *in vivo*.[77] A randomised double blind study from Brazil of pentoxifylline 1·2 g daily in ENL demonstrated that it was not as effective as thalidomide 300 mg daily.[46] Published small case series show a limited response of ENL to pentoxifylline at daily doses ranging from 1200–2400 mg.[78–81]

Aspirin and indomethacin

Aspirin has been evaluated in the treatment of ENL in three double blind controlled trials and indomethacin in one. In one study both were less effective than Prednisolone[82] and in another trial aspirin was less effective than thalidomide.[49] In the third study aspirin was compared with colchicine in the management of ENL and both were equally effective in mild disease.[83]

Cyclosporin

The role of cyclosporin in ENL was thought to be promising following *in vitro* studies, but published clinical data are restricted to a short series of three patients in whom it was largely effective.[84,85]

Methotrexate[86] and azathioprine.[28]

Both have both been reported to be useful in the management of refractory ENL when used in conjunction with systemic steroids. Both men and women are advised not to start a pregnancy while on methotrexate and for 6 months after stopping it. Azathioprine appears to be safe in pregnancy.[87]

Zafirlukast

The leukotriene antagonist zafirlukast has been tried in an open phase II cohort trial using an initial dose of 40 mg twice daily. It was effective in six patients with ENL although outcome measures were not defined.[88]

Infliximab

The successful use of this chimeric monoclonal antibody, which suppresses the biological activity of TNF by specifically binding to it, has been reported in a single case of recurrent ENL treated in the Netherlands.[89]

Colchicine

Treatment with colchicine appeared beneficial in two small case series.[90,91] A subsequent controlled study of five patients failed to demonstrate any impact of colchicine on steroid requirement.[92] A second controlled study comparing colchicine with aspirin showed a marginal benefit in moderate disease.[83]

Chloroquine

Chloroquine is used to manage ENL but there is little evidence from controlled studies that it is effective.[82] Chloroquine produced quicker improvement of neuritis than indomethacin and aspirin in a small double blind study.[49]

Zinc

Oral zinc (220 mg per day) has been used in two small uncontrolled studies from India that reported reduced steroid requirements but it is not possible to make any definite conclusions about the clinical effect.[93,94]

The challenge of ENL

ENL reactions are usually recurrent or chronic and predicting which clinical pattern an individual's disease will follow is not possible.[6] This poses a problem in deciding which therapy to institute in the early stages of the disease. A person who will require numerous or prolonged courses of high dose steroids might possibly be managed differently from the outset if such a prognosis were predictable. It has also been reported that patients treated initially with steroids have a reduced response when changed to thalidomide but this has never been formally tested and would be difficult to test.

The algorithm in Figure 2 is a suggested approach to the management of moderate and severe ENL starting with prednisolone or thalidomide. It is not logical routinely to use thalidomide and oral corticosteroids together to manage ENL. The available evidence does not support this and patients are exposed to the potential adverse effects of both drugs.

The ILEP guidelines advocate considering using thalidomide for severe ENL if treatment with corticosteroids and clofazimine is not effective. The duration of treatment required for adequate management of ENL is uncertain regardless of which anti-reactional therapy is used. The anxiety provoked by long-term immunosuppression or exposure to toxic drugs is exacerbated by the frustration of relapse as therapy is tapered.

Individuals who require long-term corticosteroid therapy should be considered for steroid sparing agents or therapies which may obviate the need for steroids. The adverse effects of steroids may require dose reduction or discontinuation. Rarely there may be an absolute contraindication to corticosteroids or tachyphylaxis to steroids may develop.

Deciding which alternative agents to use will be guided by availability, patient preferences and specific risks associated with individual treatments. The individuals requiring a second line agent are likely to need it for many months to prevent recurrence.

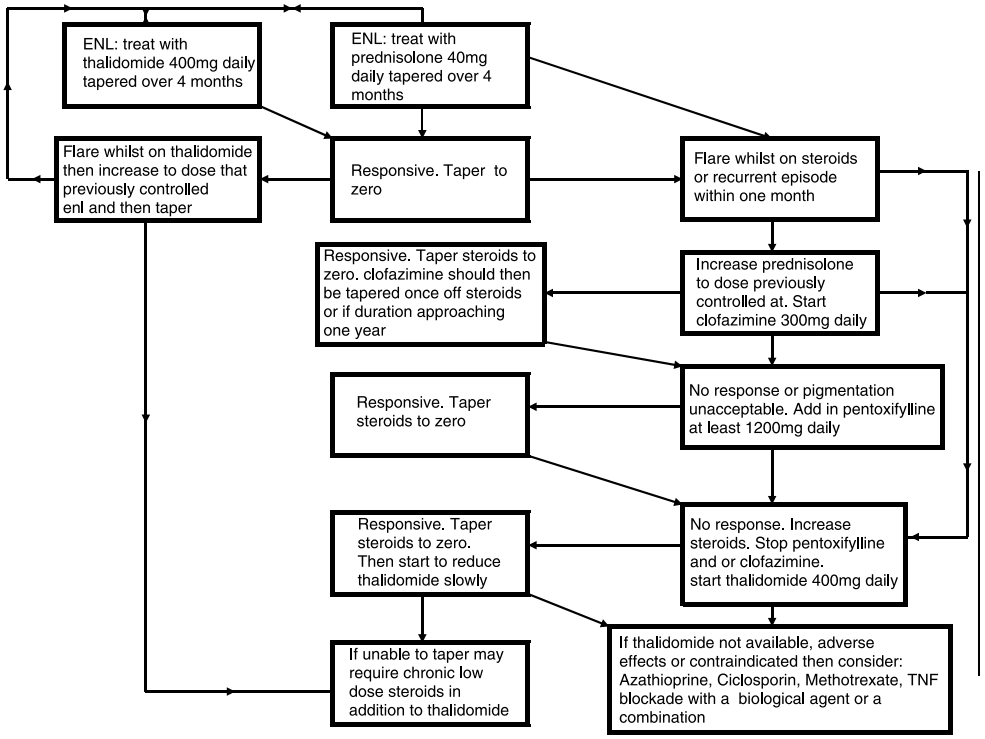

Figure 2. Algorithm for managing moderate and severe ENL.

Future Directions

There is a need for further research in the management of ENL, acknowledging that it is difficult to perform trials in a condition which spontaneously fluctuates. Topics that need urgent attention include:

1. The development of a validated scale for measuring ENL reactions.
2. A direct comparison of thalidomide and corticosteroids in the management of ENL. Given the recurrent nature of ENL any such study should use time to next episode of ENL as an outcome measure as well as the response of clinical parameters. A comparison of thalidomide alone versus a combination of thalidomide and prednisolone using nerve pain, nerve tenderness and nerve function impairment as outcome measures is also warranted.
3. An assessment of the neurotoxicity of thalidomide in leprosy patients and its clinical relevance in a situation where uncontrolled ENL may itself cause permanent neuropathy.[95] It is unclear why leprologists have failed to pick up clinically relevant neuropathy associated with the use of thalidomide.
4. The implementation of the robust patient monitoring schemes that already exist and are vital to prevent thalidomide embryopathy. The 34 cases of thalidomide embryopathy born between 1965 and 1996 in South America show a continuing need for improvement.[96]

National programmes and organisations involved in the delivery of leprosy care should develop a consensus on the role of thalidomide in the management of ENL and the safest way to use the drug in leprosy endemic settings. Quality of life studies in patients with ENL would help to determine the social and financial impact of this condition, and the socio-economic importance of effective control.

Conflict of interests

DNJL was a paid adviser to Pharmion during their application to the European Medicines Agency to have thalidomide licensed for use in the treatment of erythema nodosum leprosum.

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