

Leprosy type 1 reactions and erythema nodosum leprosum* *Reações hansênicas do tipo 1 e eritema nodoso hansênico**

Indira P. Kahawita¹Stephen L. Walker²Diana N.J. Lockwood³

Abstract: Leprosy reactions are a major cause of nerve damage and morbidity in a significant proportion of leprosy patients. Reactions are immunologically mediated and can occur even after successful completion of multi-drug therapy. This review focuses on the epidemiology, pathology and treatment of leprosy type 1 reactions, erythema nodosum leprosum and silent neuropathy.

Keywords: Erythema nodosum; Leprosy; Leprosy/complications; Leprosy/therapy; Neuritis; Peripheral nervous system diseases

Resumo: As reações hansênicas são a principal causa de dano e morbidade neural em grande parte dos pacientes hansênicos. São imunomediadas e podem ocorrer mesmo após o término bem sucedido da poliquimioterapia. Esta revisão enfoca a epidemiologia, a patologia e o tratamento das reações hansênicas do tipo 1, do eritema nodoso hansênico e da neuropatia silenciosa.

Palavras-chave: Doenças do sistema nervoso periférico; Eritema nodoso; Hanseníase; Hanseníase/complicações; Hanseníase/terapia; Neurite

INTRODUCTION

Leprosy reactions are immunological phenomena that occur before, during or after the completion of multi-drug therapy (MDT). They contribute immensely to the burden of leprosy and need to be diagnosed and treated early to prevent nerve function impairment and permanent disability.

Dermatologists have an increasingly important role to play in the management of leprosy with the integration of leprosy services into general medical services worldwide.

Two major complications of leprosy are type 1 reactions (T1R) and erythema nodosum leprosum (ENL). These distinct conditions occur separately but may arise at different times in the same patient.^{1,2} It is important to recognise that both these conditions can result in permanent loss of nerve function. Nerve function impairment (NFI) is defined as any reduction in sensory or motor function. Neuritis (inflammation of the peripheral nerve trunks) may or may not be accompanied by clinically detectable NFI.

TYPE 1 (REVERSAL) REACTIONS

A T1R is characterised by the development of acute inflammation in skin lesions or nerves or both.³ Borderline leprosy is a strong risk factor for the occurrence of T1Rs⁴ but individuals with polar forms of leprosy may also experience T1Rs. The onset of a T1R may be very rapid. T1Rs are frequently recurrent and this can lead to further nerve damage.⁵

Skin lesions become acutely inflamed and oedematous and may ulcerate. Oedema of the hands, feet and face can also be a feature of a reaction but systemic symptoms are unusual.

Acute neuritis leads to NFI which if not treated rapidly and adequately leads to permanent loss of nerve function causing peripheral sensory and/or motor neuropathy.

Skin lesions develop scaling in the chronic phase of T1R and may then mimic psoriasis, dermatophyte infections and cutaneous T-cell lymphoma.⁶

T1Rs may rarely occur many years after

Approved by the Editorial Board and accepted for publication on December 28, 2007.

* Work done at Department of Infectious and Tropical Diseases; London School of Hygiene and Tropical Medicine – London, United Kingdom.

Conflict of interest/Conflito de interesse: DNJ Lockwood was a paid adviser to Pharmion in 2003 during their application to the European Medicines Agency to have thalidomide licensed for the use in the treatment of ENL.

Financial funding/Suporte financeiro: None.

¹ Clinical Research Fellow. Department of Infectious and Tropical Diseases; London School of Hygiene and Tropical Medicine – London, United Kingdom.

² Clinical Research Fellow. Department of Infectious and Tropical Diseases; London School of Hygiene and Tropical Medicine – London, United Kingdom.

³ Professor of Tropical Medicine and Head of Clinical Research. Department of Infectious and Tropical Diseases; London School of Hygiene and Tropical Medicine – London, United Kingdom.

completion of MDT. In this situation it may be difficult to distinguish between a late T1R and relapse.⁷

Epidemiology

The measured prevalence rates of T1R vary depending on whether the studies are conducted in hospital or field settings. Twenty-six per cent of Brazilian patients in Rio de Janeiro who had positive slit-skin smears experienced a T1R during the two year period they were taking MDT.⁸ A retrospective study of individuals with borderline leprosy attending a leprosy referral centre in Nepal showed that 30% developed a T1R.⁵ Half of the individuals who experienced a T1R had demonstrable new nerve function impairment.

A cohort of multibacillary (MB) patients recruited at two referral centres in north India had a prevalence rate of T1R of 19.8% at the time of first presentation.⁹ A prospective hospital based study from Vietnam found a 29.1% prevalence of T1Rs.¹⁰

Risk factors

Extensive disease and having a positive slit skin smear are risk factors for T1Rs.^{10,11} The detection of *Mycobacterium leprae* DNA by PCR in skin patches at the time of diagnosis is associated with an increased risk of T1R in Brazilian patients with a single skin lesion.¹² Increasing age has also been reported to be a risk factor for T1R in Vietnamese and Brazilians.^{10,12} Individuals who present with WHO disability grades type 1 and 2 are significantly more likely to have severe T1Rs at diagnosis.¹³ T1Rs are frequently seen after starting MDT or during the puerperium.¹⁴

Pathology of type 1 reactions

T1Rs are delayed hypersensitivity reactions.¹⁵ The dermatopathological features of acute T1R are oedema, increased number of lymphocytes in the dermis and loss of normal granuloma organisation. As time passes there is an increase in the number of Langhans' giant cells.¹⁵ A recent study of four histopathologists examining skin biopsies independently found that oedema and giant cells are the most sensitive indicators of T1R (personal communication).

M. leprae antigens have been demonstrated in the nerves and skin of patients experiencing T1Rs, localised to Schwann cells and macrophages.¹⁶

Schwann cells have been shown to express Toll-like receptor 2.¹⁷ *M. leprae* infection may lead to the expression of MHC II on the surface of the cells. This may give rise to antigen presentation which triggers CD4 lymphocyte killing of the infected cell which is mediated by cytokines such as tumour necrosis factor (TNF).¹⁸ Immunohistochemistry studies show greater

TNF staining in the skin and nerves during T1Rs compared with non-reactional controls.¹⁹ T1Rs appear to be mediated via Th1 lymphocytes and cells from reactional lesions express the pro-inflammatory cytokines interferon gamma (IFN- γ), interleukin 12 (IL-12) and the oxygen free radical producer inducible nitric oxide synthase.²⁰

Treatment of type 1 reactions

Patients should be educated about T1Rs when being commenced on MDT. They should be advised to seek help immediately if they experience any of the symptoms and signs of a T1R.

The treatment of T1Rs is aimed at controlling the acute inflammation, easing pain and reversing nerve damage. MDT should be initiated in those presenting with a T1R or continued in those who develop a reaction whilst on it.

Individuals with inflamed skin lesions, neuritis or nerve function impairment are treated with oral corticosteroids. It is our practise to treat adults with 30-40mg of prednisolone daily for one month and gradually reduce the dose by 5mg per month. At each clinic visit it is essential to assess nerve function as accurately as possible. We use Semmes-Weinstein monofilaments (which are readily available in Brazil) and voluntary motor testing to ensure that nerve function is not deteriorating.

The current WHO Global Strategy document recommends treatment of severe T1Rs with "...a course of steroids, usually lasting 3-6 months".²¹ Despite prolonged oral prednisolone only 60% will show improvement in nerve function.²² The erythema and oedema of skin lesions will readily respond.

The recent Cochrane systematic review of "Corticosteroids for treating nerve damage in leprosy" identified only three randomised controlled trials (RCT) that met the review criteria.²³ Its conclusion was that evidence was lacking and that further RCTs are needed to identify the best treatment regimens.

A randomised controlled study comparing different steroid regimes suggested that duration rather than dose of treatment with prednisolone may be more important in controlling T1Rs.²⁴ In this study individuals who received prednisolone 30 or 60 mg tapered to zero over 20 weeks required less additional prednisolone than those randomised to receive prednisolone 60mg tapered over 12 weeks. Individuals with and without nerve involvement were enrolled into the study. A limitation of the study is that the primary outcome measures were failure to respond to treatment and physician determined requirement for additional prednisolone rather than improvement in nerve function or skin signs.

Treatment with a four month course of steroids

has been used to try and prevent reactional episodes, neuritis and nerve function impairment. The prednisolone had a protective effect whilst patients were taking it but at 12 months follow up this effect had been lost.²⁵

The treatment of patients with steroids is not beneficial if their NFI has been present for longer than six months. The TRIPOD 3 study compared prednisolone with placebo and did not demonstrate any significant difference in improvement of nerve function between the two groups.²⁶

In the rare instances where it is difficult to know whether a patient is suffering from a late reaction or relapse then a therapeutic trial of corticosteroids is recommended.²¹

Azathioprine in combination with a short course of prednisolone was as effective as a 12-week course of prednisolone in the management of T1Rs in Nepal.²⁷ Cyclosporin has been used in pilot studies in Nepal, Ethiopia and Brazil with some success.^{28,29}

SILENT NEUROPATHY

Van Brakel and Khawas proposed the term "silent neuropathy" (SN) to describe the phenomenon of nerve function impairment occurring in the absence of symptoms. It is therefore only detected if physicians perform a careful examination of the peripheral nervous system. In Nepal 13% of patients developed SN. The majority of SN was present at diagnosis or developed during the first year of MDT.³⁰

The treatment of SN is the same as for T1R. The duration of SN can not be ascertained from the history and we have a low threshold for giving a course of oral prednisolone.

ERYTHEMA NODOSUM LEPROSUM

ENL or type 2 reaction is a serious, difficult to manage immunological complication of borderline lepromatous (BL) and lepromatous leprosy (LL). The majority of patients with ENL go on to develop several episodes over many years, as multiple acute episodes or chronic ENL.^{11,31} Less than 10% of patients in a large cohort in India had only a single episode of ENL while 62.5% had chronic ENL.³¹

The cutaneous manifestation of ENL is widespread crops of erythematous, inflamed nodules and papules, which may be superficial or deep.³ Ulcerated, necrotic, pustular and bullous forms have also been reported. Some nodules may persist as a chronic painful panniculitis leading to fibrosis and scarring.³

Neuritis, in the form of painful enlarged nerves and nerve function impairment, may occur as part of ENL. The neuritis may be less dramatic than in T1R but it is important to recognise nerve involvement early to prevent permanent loss of function.

ENL may present as a systemic illness, with high fever, systemic upset and prostration. Peripheral oedema and transient proteinuria can also occur. Iritis and episcleritis can occur and may be sight threatening. Other features such as pain, photophobia and lacrimation may be absent.³ Orchitis, lymphadenopathy, organomegaly, joint involvement, dactylitis and bone tenderness, especially over the tibia, are well recognised features of ENL.

Differential diagnosis

ENL should be considered in the differential diagnosis of erythema nodosum and other forms of panniculitis. ENL lesions differ from erythema nodosum by their evanescent nature and the large number of lesions involving sites other than the lower legs. ENL may also mimic Sweet's syndrome and septicaemia.⁶

Bullous ENL can be considered in the differential diagnosis of immunobullous disorders. Ulcerated lesions should be differentiated from pyoderma gangrenosum. Chronic ENL may also mimic connective tissue disorders or lymphoreticular malignancies.

A slit skin smear is a useful investigation which will rapidly confirm the presence of acid fast bacilli in the skin in ENL.⁶

Epidemiology and risk factors

There is wide geographic variation in the prevalence of ENL reactions. In Brazil 37% of new BL and LL cases experience ENL.⁸ In Asia reported figures vary between 19-26% of BL and LL cases in Nepal, India and Thailand.^{8,13,31,32}

ENL reactions occur most commonly during the first year of MDT.³¹⁻³³ One third of patients with ENL have the diagnosis of leprosy made at the same time as their reaction.^{32,33}

Lepromatous leprosy (LL) and a bacillary index (BI) greater than 4+ have been shown to be risk factors for ENL.^{31,32} Pregnancy, lactation, puberty, intercurrent infection, vaccination and psychological stress have been considered to precipitate ENL³ but these associations have not been confirmed in prospective studies.

Pathology of erythema nodosum leprosum

The inflammatory infiltrate in ENL is situated in the dermis and the subcutis. The constituent cells vary with the timing of the skin biopsy. In acute lesions where skin biopsy is performed within 72 hours of occurrence, the predominant cell type is the neutrophil. Eosinophils and mast cells may also be present.³⁴ Skin biopsies performed later show fewer neutrophils and increasing numbers of lymphocytes, plasma cells and histiocytes, representing a chronic inflammatory infiltrate.

The other histological features reported in ENL

are oedema of the dermis and subcutis, vasculitis and panniculitis.³⁴ Changes due to leprosy will also be evident. The infiltrate due to LL may contain histiocytes with fatty change and foamy cells arranged diffusely. In biopsies from patients with BL leprosy the granuloma may contain histiocytes and lymphocytes.³⁵ In both cases large numbers of acid fast bacilli, usually granular in appearance, will be found.

Immune complexes are important in the pathogenesis of ENL as demonstrated by the presence of complexes of complement and *M. leprae* antigen in cutaneous lesions.^{36,37} High levels of circulating TNF have been found in some individuals with ENL.³⁸ There is evidence of a cell mediated immune response in the pathogenesis of ENL. The major T cell subtype in ENL is the CD4+ cell in contrast to lepromatous leprosy where CD8+ cells predominate.^{39,40} TNF and IL-6 have been shown to be present in skin lesions of ENL while IL-4 is absent or low⁴¹⁻⁴³ which supports a role for Th1 type T cells.

Treatment of erythema nodosum leprosum

The main aims in the management of ENL are the control of inflammation, pain relief and prevention of further episodes.⁴⁴ Mild cases of ENL can be treated with non steroidal anti-inflammatory drugs (NSAIDs).

● Corticosteroids

Prednisolone is commonly used for the management of moderate to severe ENL. The WHO Global Strategy document does not give specific advice concerning the dosage of prednisolone.²¹ We commonly start at a dose of prednisolone 40-60mg daily but some leprologists use higher initial doses. The dose of prednisolone should be slowly reduced according to response. The majority of patients require multiple or prolonged courses of prednisolone due to the natural history of the condition.³¹ Tachyphylaxis to prednisolone may also develop.

● Concerns about the use of corticosteroids in the management of reactions

The use of potent immunosuppressants is potentially problematic in areas endemic for severe infections such as tuberculosis. Immunosuppression may also lead to fatal strongyloidiasis.⁴⁵

Analysis of the adverse events attributable to prednisolone in the three TRIPOD trials suggests that the drug is safe when used under field conditions in standardised regimes.⁴⁶ The trials used a total prednisolone dose of 1.96g and 2.52g. The steroid treated group were significantly more likely to experience minor adverse events but there was no difference in the likelihood of major adverse events between the prednisolone and placebo groups. Three

hundred of the 815 patients enrolled in the three studies were followed for 24 months and none developed tuberculosis or hypertension during that time.

The long term adverse effects of corticosteroid therapy in individuals with leprosy reactions have not been studied. The amount of diabetes, cataract and hypertension experienced by this group is not known.

It has been reported that patients receiving steroids for ENL develop more adverse effects compared to those with T1Rs which may be due to the longer duration of treatment in this group.⁴⁷

● Thalidomide

Thalidomide is very effective in the treatment of moderate to severe ENL. It has a rapid onset of action. Its beneficial effect is thought to be due to its action on TNF but other mechanisms may also play a part.⁴⁸ Prospective clinical trials have shown that treatment with thalidomide has a quicker action of onset and reduces the number of skin lesions, fever and systemic symptoms better than pentoxifylline, aspirin and placebo.⁴⁹⁻⁵² Treatment with thalidomide has also been shown to reduce the prednisolone requirement of patients with chronic ENL.⁵³

We suggest using a starting dose of 400mg thalidomide at night in severe ENL and to reduce the dose to 300mg as soon as possible. This dose can then be reduced by 100mg per month but a maintenance dose may be required in those with chronic disease.⁵⁴

Thalidomide should be used with extreme caution due to its teratogenic potential. The System for Thalidomide Education and Prescribing Safety (STEPS) programme adopted by the FDA in the USA has been shown to be very effective in preventing pregnancies in women taking thalidomide.⁵⁵ There has been a recent report of three cases of thalidomide embryopathy in Brazil and importantly tablet sharing was a major contributory factor.⁵⁶

Women of child bearing potential who require thalidomide should be provided with information about its adverse effects and counselled on the importance of the need to avoid pregnancy. A negative pregnancy test should be obtained before starting thalidomide therapy and two methods of contraception should be prescribed. The pregnancy test should be repeated every month. Only one month's supply of thalidomide should be prescribed.⁵⁴ In many leprosy endemic countries such stringent arrangements are not possible.

Somnolence and dizziness are the commonest adverse affects of thalidomide. Cutaneous adverse effects occur in 3% of individuals⁵⁷ and may be exanthems or rarely erythema multiforme and toxic epidermal necrolysis.⁵⁸ Thalidomide causes a peripheral neuropathy but there are no data regarding thalidomide-induced

neuropathy in patients with ENL. Deterioration of nerve function in patients receiving thalidomide should not be assumed to be due to their leprosy.

● Clofazimine

Clofazimine is a mild anti-inflammatory agent. It can be used for the treatment of mild to moderate ENL but has a slow onset of action.⁵⁹ The clofazimine component of MB MDT probably reduces the incidence of ENL but this has not been formally tested.⁶⁰ Clofazimine at a dose of up to 300mg daily can be given to help control ENL. It is complicated by increased pigmentation and the possibility of clofazimine crystal enteropathy.^{61,62} This higher dose should not be continued for more than 12 months.

● Other drugs

A recent Brazilian double blind RCT has shown that pentoxifylline is inferior to thalidomide in controlling cutaneous and systemic features of ENL. The pentoxifylline was also less well tolerated.⁴⁹ Colchicine and chloroquine have been evaluated in small studies and their effect was marginal. There are case reports and case series on the use azathioprine,⁶³ methotrexate,⁶⁴ oral zinc,⁶⁵ and the chimeric anti-TNF monoclonal antibody, infliximab,⁶⁶ for the treatment of ENL.

HIV AND LEPROSY REACTIONS

There is limited evidence from Uganda that T1Rs may occur more frequently in individuals with HIV and *M. leprae* co-infection⁶⁷ but this effect has not been replicated by studies from India or Mali although different methodologies were employed.^{68,69}

T1Rs presenting as immune reconstitution disease in HIV positive individuals commenced on anti-retroviral therapy (ART) have been reported.^{70,71}

There is no evidence to guide physicians in the optimal use of immunosuppression to manage T1Rs affecting HIV positive individuals. The current treatment of T1Rs in co-infected individuals is with corticosteroids as it is in HIV negative patients. The reported cases of T1Rs in co-infected individuals, whether ART related or not, have all been treated with corticosteroids. One individual required the introduction of azathioprine to control repeated

relapses of his steroid dependent T1R.⁷²

The adverse effect of additional immunosuppression in HIV positive patients with T1Rs is an obvious concern but there is no evidence to inform decisions about dose and duration of treatment in this group.

There are no good data on the effect of HIV infection on the frequency or clinical presentation of ENL in co-infected patients.

QUALITY OF LIFE, DISABILITY AND SOCIOECONOMIC IMPACT OF LEPROSY REACTIONS

The impact of leprosy reactions on quality of life and socioeconomic factors has not been formally assessed. The majority of work looking at disability due to leprosy has studied NFI in the context of MDT and not specifically reactions. It is widely accepted that reactions are important in the causation of disability.

Ocular complications due to reactions can lead to blindness. The presence of potentially blinding leprosy-related eye disease is associated with "reaction involving the face."⁷³

CONCLUSION

The management of leprosy reactions and silent neuropathy continues to be a major challenge. The prompt diagnosis and effective treatment of these complications of leprosy are essential if nerve function impairment, deformity and disability are to be minimised. □

Acknowledgements

Dr Kahawita is supported by a Training Fellowship from the Ministry of Health, Sri Lanka. Dr Walker is supported by grants from LEPRO, the American Leprosy Mission, the Special Trustees of the Hospital for Tropical Diseases, London and the Geoffrey Dowling Fellowship of the British Association of Dermatologists.

REFERENCES

1. Rea TH, Sieling PA. Delayed-type hypersensitivity reactions followed by erythema nodosum leprosum. *Int J Lepr Other Mycobact Dis.* 1998;66:316-27.
2. Moraes MO, Sampaio EP, Nery JA, Saraiva BC, Alvarenga FB, Sarno EN. Sequential erythema nodosum leprosum and reversal reaction with similar lesional cytokine mRNA patterns in a borderline leprosy patient. *Br J Dermatol.* 2001;144:175-81.
3. Pfaltzgraff RE, Ramu G. Clinical leprosy. In: Hastings RC, editor. *Leprosy.* 2nd ed. Edinburgh: Churchill Livingstone; 1994. p. 237-90.
4. Lienhardt C, Fine PE. Type 1 reaction, neuritis and disability in leprosy. What is the current epidemiological situation? *Lepr Rev.* 1994;65:9-33.
5. Van Brakel WH, Khawas IB, Lucas SB. Reactions in leprosy: an epidemiological study of 386 patients in west Nepal. *Lepr Rev.* 1994;65:190-203.
6. Nunzi E, Fiallo P. Differential diagnosis. In: Hastings RC, editor. *Leprosy.* 2nd ed. Edinburgh: Churchill Livingstone; 1994. p. 291-316.
7. Waters MF. Distinguishing between relapse and late reversal reaction in multidrug (MDT)-treated BT leprosy. *Lepr Rev.* 2001;72:250-3.
8. Nery JA, Vieira LM, de Matos HJ, Gallo ME, Sarno EN. Reactional states in multibacillary hansen disease patients during multidrug therapy. *Rev Inst Med Trop Sao Paulo.* 1998;40:363-70.
9. van Brakel WH, Nicholls PG, Das L, Barkataki P, Suneetha SK, Jadhav RS, et al. The INFIR Cohort Study: investigating prediction, detection and pathogenesis of neuropathy and reactions in leprosy. Methods and baseline results of a cohort of multibacillary leprosy patients in north India. *Lepr Rev.* 2005;76:14-34.
10. Ranque B, Nguyen VT, Vu HT, Nguyen TH, Nguyen NB, Pham XK, et al. Age is an important risk factor for onset and sequelae of reversal reactions in Vietnamese patients with leprosy. *Clin Infect Dis.* 2007;44:33-40.
11. Kumar B, Dogra S, Kaur I. Epidemiological characteristics of leprosy reactions: 15 years experience from north India. *Int J Lepr Other Mycobact Dis.* 2004;72:125-33.
12. Sousa AL, Stefani MM, Pereira GA, Costa MB, Rebello PF, Gomes MK, et al. *Mycobacterium leprae* DNA Associated with type 1 reactions in single lesion paucibacillary leprosy treated with single dose Rifampin, Ofloxacin, and Minocycline. *Am J Trop Med Hyg.* 2007;77:829-33.
13. Schreuder PA. The occurrence of reactions and impairments in leprosy: experience in the leprosy control program of three provinces in northeastern Thailand, 1987-1995 [correction of 1978-1995]. II. Reactions. *Int J Lepr Other Mycobact Dis.* 1998;66:159-69.
14. Lockwood DN, Sinha HH. Pregnancy and leprosy: a comprehensive literature review. *Int J Lepr Other Mycobact Dis.* 1999;67:6-12.
15. Job CK. Pathology of leprosy. In: Hastings RC, editor. *Leprosy.* 2nd ed. Edinburgh: Churchill Livingstone; 1994. p. 193-234.
16. Lockwood DN, Colston MJ, Khanolkar-Young SR. The detection of *Mycobacterium leprae* protein and carbohydrate antigens in skin and nerve from leprosy patients with type 1 (reversal) reactions. *Am J Trop Med Hyg.* 2002;66:409-15.
17. Oliveira RB, Ochoa MT, Sieling PA, Rea TH, Rambukkana A, Sarno EN, et al. Expression of Toll-like receptor 2 on human Schwann cells: a mechanism of nerve damage in leprosy. *Infect Immun.* 2003;71:1427-33.
18. Ochoa MT, Stenger S, Sieling PA, Thoma-Uszynski S, Sabet S, Cho S, et al. T-cell release of granulysin contributes to host defense in leprosy. *Nat Med.* 2001;7:174-9.
19. Khanolkar-Young S, Rayment N, Brickell PM, Katz DR, Vinayakumar S, Colston MJ, et al. Tumour necrosis factor-alpha (TNF-alpha) synthesis is associated with the skin and peripheral nerve pathology of leprosy reversal reactions. *Clin Exp Immunol.* 1995;99:196-202.
20. Little D, Khanolkar-Young S, Coulthart A, Suneetha S, Lockwood DN. Immunohistochemical analysis of cellular infiltrate and gamma interferon, interleukin-12, and inducible nitric oxide synthase expression in leprosy type 1 (reversal) reactions before and during prednisolone treatment. *Infect Immun.* 2001;69:3413-7.
21. World Health Organization [homepage on the Internet]. Global strategy for further reducing leprosy burden and sustaining leprosy control activities (2006-2010): Operational guidelines. [cited 2007 Dec 12]. Available from: <http://www.who.int/lep/resources/SEAGLP20062.pdf>
22. Van Brakel WH, Khawas IB. Nerve function impairment in leprosy: an epidemiological and clinical study--Part 2: Results of steroid treatment. *Lepr Rev.* 1996;67:104-18.
23. Van Veen NH, Nicholls PG, Smith WC, Richardus JH. Corticosteroids for treating nerve damage in leprosy. *Cochrane Database Syst Rev.* 2007:CD005491.
24. Rao PS, Sugamaram DS, Richard J, Smith WC. Multi-centre, double blind, randomized trial of three steroid regimens in the treatment of type-1 reactions in leprosy. *Lepr Rev.* 2006;77:25-33.
25. Smith WC, Anderson AM, Withington SG, Van Brakel WH, Croft RP, Nicholls PG, et al. Steroid prophylaxis for prevention of nerve function impairment in leprosy: randomised placebo controlled trial (TRIPOD 1). *BMJ.* 2004;328:1459.
26. Richardus JH, Withington SG, Anderson AM, Croft RP, Nicholls PG, Van Brakel WH, et al. Treatment with corticosteroids of long-standing nerve function impairment in leprosy: a randomized controlled trial (TRIPOD 3). *Lepr Rev.* 2003;74:311-8.
27. Marlowe SN, Hawksworth RA, Butlin CR, Nicholls PG, Lockwood DN. Clinical outcomes in a randomized controlled study comparing azathioprine and prednisolone versus prednisolone alone in the treatment of severe leprosy type 1 reactions in Nepal. *Trans R Soc Trop Med Hyg.* 2004;98:602-9.
28. Marlowe SN, Leekassa R, Bizuneh E, Knuutila J, Ale P, Bhattarai B, et al. Response to ciclosporin treatment in Ethiopian and Nepali patients with severe leprosy

- Type 1 reactions. *Trans R Soc Trop Med Hyg.* 2007;101:1004-12.
29. Sena CB, Salgado CG, Tavares CM, Da Cruz CA, Xavier MB, Do Nascimento JL. Cyclosporine A treatment of leprosy patients with chronic neuritis is associated with pain control and reduction in antibodies against nerve growth factor. *Lepr Rev.* 2006;77:121-9.
 30. Van Brakel WH, Khawas IB. Silent neuropathy in leprosy: an epidemiological description. *Lepr Rev.* 1994;65:350-60.
 31. Pocaterra L, Jain S, Reddy R, Muzaffarullah S, Torres O, Suneetha S, et al. Clinical course of erythema nodosum leprosum: an 11-year cohort study in Hyderabad, India. *Am J Trop Med Hyg.* 2006;74:868-79.
 32. Manandhar R, LeMaster JW, Roche PW. Risk factors for erythema nodosum leprosum. *Int J Lepr Other Mycobact Dis.* 1999;67:270-8.
 33. Becx-Bleumink M, Berhe D. Occurrence of reactions, their diagnosis and management in leprosy patients treated with multidrug therapy; experience in the leprosy control program of the All Africa Leprosy and rehabilitation training center (ALERT) in Ethiopia. *Int J Lepr Other Mycobact Dis.* 1992;60:173-84.
 34. Mabalay MC, Helwig EB, Tolentino JG, Binford CH. The Histopathology and histochemistry of erythema nodosum leprosum. *Int J Lepr.* 1965 Jan-Mar;33:28-49.
 35. Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. *Int J Lepr Other Mycobact Dis.* 1966;34:255-73.
 36. Wemambu SN, Turk JL, Waters MF, Rees RJ. Erythema nodosum leprosum: a clinical manifestation of the arthus phenomenon. *Lancet.* 1969;2:933-5.
 37. Ridley MJ, Ridley DS. The immunopathology of erythema nodosum leprosum: the role of extravascular complexes. *Lepr Rev.* 1983;54:95-107.
 38. Sarno EN, Grau GE, Vieira LM, Nery JA. Serum levels of tumour necrosis factor-alpha and interleukin-1 beta during leprosy reactional states. *Clin Exp Immunol.* 1991;84:103-8.
 39. Modlin RL, Mehra V, Jordan R, Bloom BR, Rea TH. In situ and in vitro characterization of the cellular immune response in erythema nodosum leprosum. *J Immunol.* 1986;136:883-6.
 40. Modlin RL, Gebhard JF, Taylor CR, Rea TH. In situ characterization of T lymphocyte subsets in the reactional states of leprosy. *Clin Exp Immunol.* 1983;53:17-24.
 41. Moraes MO, Sarno EN, Almeida AS, Saraiva BC, Nery JA, Martins RC, et al. Cytokine mRNA expression in leprosy: a possible role for interferon-gamma and interleukin-12 in reactions (RR and ENL). *Scand J Immunol.* 1999;50:541-9.
 42. Nath I, Vemuri N, Reddi AL, Bharadwaj M, Brooks P, Colston MJ, et al. Dysregulation of IL-4 expression in lepromatous leprosy patients with and without erythema nodosum leprosum. *Lepr Rev.* 2000;71(Suppl):S130-7.
 43. Teles RM, Moraes MO, Geraldo NT, Salles AM, Sarno EN, Sampaio EP. Differential TNFalpha mRNA regulation detected in the epidermis of leprosy patients. *Arch Dermatol Res.* 2002;294:355-62.
 44. Lockwood DN. The management of erythema nodosum leprosum: current and future options. *Lepr Rev.* 1996;67:253-9.
 45. Leang B, Lynen L, Tootill R, Griffiths S, Monchy D. Death caused by strongyloides hyperinfection in a leprosy patient on treatment for a type II leprosy reaction. *Lepr Rev.* 2004;75:398-403.
 46. Richardus JH, Withington SG, Anderson AM, Croft RP, Nicholls PG, Van Brakel WH, et al. Adverse events of standardized regimens of corticosteroids for prophylaxis and treatment of nerve function impairment in leprosy: results from the 'TRIPOD' trials. *Lepr Rev.* 2003;74:319-27.
 47. Sugumaran DS. Leprosy reactions--complications of steroid therapy. *Int J Lepr Other Mycobact Dis.* 1998;66:10-5.
 48. Tadesse A, Abebe M, Bizuneh E, Mulugeta W, Aseffa A, Shannon EJ. Effect of thalidomide on the expression of TNF-alpha mRNA and synthesis of TNF-alpha in cells from leprosy patients with reversal reaction. *Immunopharmacol Immunotoxicol.* 2006;28:431-41.
 49. Sales AM, Matos HJ, Nery JA, Duppre NC, Sampaio EP, Sarno EN. Double-blind trial of the efficacy of pentoxifylline vs thalidomide for the treatment of type II reaction in leprosy. *Braz J Med Biol Res.* 2007;40:243-8.
 50. Iyer CG, Languillon J, Ramanujam K, Tarabini-Castellani G, De las Aguas JT, Bechelli LM, et al. WHO co-ordinated short-term double-blind trial with thalidomide in the treatment of acute lepra reactions in male lepromatous patients. *Bull World Health Organ.* 1971;45:719-32.
 51. Pearson JM, Vedagiri M. Treatment of moderately severe erythema nodosum leprosum with thalidomide-a double-blind controlled trial. *Lepr Rev.* 1969;40:111-6.
 52. Sheskin J. Thalidomide in the treatment of lepra reactions. *Clin Pharmacol Ther.* 1965;6:303-6.
 53. Waters MF. An internally-controlled double blind trial of thalidomide in severe erythema nodosum leprosum. *Lepr Rev.* 1971;42:26-42.
 54. Walker SL, Waters MF, Lockwood DN. The role of thalidomide in the management of erythema nodosum leprosum. *Lepr Rev.* 2007;78:197-215.
 55. Lary JM, Daniel KL, Erickson JD, Roberts HE, Moore CA. The return of thalidomide: can birth defects be prevented? *Drug Saf.* 1999;21:161-9.
 56. Schuler-Faccini L, Soares RC, de Sousa AC, Maximino C, Luna E, Schwartz IV, et al. New cases of thalidomide embryopathy in Brazil. *Birth Defects Res A Clin Mol Teratol.* 2007;79:671-2.
 57. Glasmacher A, Hahn C, Hoffmann F, Naumann R, Goldschmidt H, von Lilienfeld-Toal M, et al. A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. *Br J Haematol.* 2006;132:584-93.
 58. Wu JJ, Huang DB, Pang KR, Hsu S, Tying SK. Thalidomide: dermatological indications, mechanisms of action and side-effects. *Br J Dermatol.* 2005;153:254-73.

59. Helmy HS, Pearson JM, Waters MF. Treatment of moderately severe erythema nodosum leprosum with clofazimine--a controlled trial. *Lepr Rev.* 1971;42:167-77.
60. Cellona RV, Fajardo TT Jr, Kim DI, Hah YM, Ramasoota T, Sampattavanich S, et al. Joint chemotherapy trials in lepromatous leprosy conducted in Thailand, the Philippines, and Korea. *Int J Lepr Other Mycobact Dis.* 1990;58:1-11.
61. Jopling WH. Complications of treatment with clofazimine (Lamprene: B663). *Lepr Rev.* 1976;47:1-3.
62. Mason GH, Ellis-Pegler RB, Arthur JF. Clofazimine and eosinophilic enteritis. *Lepr Rev.* 1977;48:175-80.
63. Verma KK, Srivastava P, Minz A, Verma K. Role of azathioprine in preventing recurrences in a patient of recurrent erythema nodosum leprosum. *Lepr Rev.* 2006;77:225-9.
64. Kar BR, Babu R. Methotrexate in resistant ENL. *Int J Lepr Other Mycobact Dis.* 2004;72:480-2.
65. Mahajan PM, Jadhav VH, Patki AH, Jogaikar DG, Mehta JM. Oral zinc therapy in recurrent erythema nodosum leprosum: a clinical study. *Indian J Lepr.* 1994;66:51-7.
66. Faber WR, Jensema AJ, Goldschmidt WF. Treatment of recurrent erythema nodosum leprosum with infliximab. *N Engl J Med.* 2006;355:739.
67. Bwire R, Kawuma HJ. Type 1 reactions in leprosy, neuritis and steroid therapy: the impact of the human immunodeficiency virus. *Trans R Soc Trop Med Hyg.* 1994;88:315-6.
68. Hussain T, Sinha S, Kulshreshtha KK, Katoch K, Yadav VS, Sengupta U, et al. Seroprevalence of HIV infection among leprosy patients in Agra, India: trends and perspective. *Int J Lepr Other Mycobact Dis.* 2005;73:93-9.
69. Lienhardt C, Kamate B, Jamet P, Tounkara A, Faye OC, Sow SO, et al. Effect of HIV infection on leprosy: a three-year survey in Bamako, Mali. *Int J Lepr Other Mycobact Dis.* 1996;64:383-91.
70. Ustianowski AP, Lawn SD, Lockwood DN. Interactions between HIV infection and leprosy: a paradox. *Lancet Infect Dis.* 2006;6:350-60.
71. Trindade MA, Manini MI, Masetti JH, Leite MA, Takahashi MD, Naafs B. Leprosy and HIV co-infection in five patients. *Lepr Rev.* 2005;76:162-6.
72. Lawn SD, Wood C, Lockwood DN. Borderline tuberculoid leprosy: an immune reconstitution phenomenon in a human immunodeficiency virus-infected person. *Clin Infect Dis.* 2003;36:e5-6.
73. Courtright P, Daniel E, Sundarrao, Ravanee J, Mengistu F, Belachew M, et al. Eye disease in multibacillary leprosy patients at the time of their leprosy diagnosis: findings from the Longitudinal Study of Ocular Leprosy (LOSOL) in India, the Philippines and Ethiopia. *Lepr Rev.* 2002;73:225-38.

MAILING ADDRESS/ENDEREÇO PARA CORRESPONDÊNCIA:

Diana Lockwood

Department of Infectious and Tropical Diseases

London School of Hygiene and Tropical Medicine

Keppel St - London WC1E 7HT

United Kingdom

E-mail: diana.lockwood@lshtm.ac.uk

How to cite this article / Como citar este artigo: Kahawita IP, Walker SL, Lockwood DNJ. Leprosy type 1 reactions and erythema nodosum leprosum. *An Bras Dermatol.* 2008;83(1):75-82.