

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Walker, SL; Lockwood, DN (2008) Leprosy type 1 (reversal) reactions and their management. *Leprosy review*, 79 (4). pp. 372-86. ISSN 0305-7518

Downloaded from: <http://researchonline.lshtm.ac.uk/5715/>

DOI:

Usage Guidelines

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: Copyright the publishers

REVIEW

Leprosy Type 1 (reversal) reactions and their management

STEPHEN L. WALKER & DIANA N.J. LOCKWOOD

Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel St, London WC1E 7HT, UK

Accepted for publication 2 December 2008

Summary The type of leprosy that affects an individual depends on the immune response mounted against the organism. This leads to a spectrum of disease which may be complicated by immunological phenomena called reactions. Antimicrobial chemotherapy is effective in treating the *Mycobacterium leprae* infection but up to 30% of individuals with borderline disease experience Type 1 reactions (T1Rs). T1Rs are immunologically mediated episodes, localised in skin and nerves, which are a major cause of nerve function impairment. Nerve function impairment may result in disability and deformity. We review the frequency and features of Type 1 reactions. The data from the limited number of randomised controlled trials of treatment are discussed. These four randomised controlled trials were all conducted in south Asia. The accepted treatment of T1Rs is with oral corticosteroids but there is no consensus about the dose or duration of treatment due to the lack of data. One randomised controlled trial showed that patients treated with a 5 month course of prednisolone (total dose 2.31 g) were less likely to need additional prednisolone than those treated with a 3 month course of prednisolone (total dose 2.94 g). This study did not use nerve function as an outcome measure. The improvement in nerve function impairment with steroid treatment is highly variable, with 33–73% of nerves recovering fully. Optimal steroid regimes and alternative treatments need to be identified if the disability associated with leprosy is to be minimised. *Search strategy* Papers for this review were identified by repeated searches of the Cochrane Clinical Trials Register, PubMed and LILACS with various combinations of the following search terms ‘leprosy’, ‘lepra’, ‘reaction’, ‘steroids’, ‘corticosteroids’, ‘reversal’, ‘Type 1’, ‘Hansen*’. Searches were complete to the end of November 2008.

Introduction

Type 1 reactions (T1Rs) are a major cause of nerve function impairment (NFI) in leprosy and affect up to 30% of susceptible individuals.¹ T1Rs may be a presenting feature of leprosy or

Correspondence to: Steve Walker, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel St, London WC1E 7HT (e-mail: drstevewalker@hotmail.com)

occur during multidrug treatment (MDT) or even after it has been completed. Corticosteroids have been used in the management of T1Rs and NFI for over 50 years but with limited data from clinical trials. The response of NFI to corticosteroids is highly variable with 33–73% of nerves recovering.^{2,3} We review the evidence for the use of corticosteroids in treating T1Rs and highlight areas where future research is needed.

TYPE 1 (REVERSAL) REACTIONS

The Ridley-Jopling classification⁴ categorises leprosy patients into a spectrum with polar tuberculoid and lepromatous forms and middle types of borderline tuberculoid (BT), mid borderline (BB) and borderline lepromatous (BL) leprosy. Patients with different disease types exhibit different immunological responses to *M. leprae*.⁵

A T1R is characterised by an increase in inflammation in skin lesions or nerves or both. T1Rs predominantly affect the borderline states of leprosy. Borderline disease is a strong risk factor for the occurrence of T1Rs¹ but small numbers of patients with the polar forms of leprosy may also experience T1Rs.⁶ Skin lesions become erythematous and/or oedematous and may ulcerate. Oedema of the hands, feet and face can also be a feature of a reaction but systemic symptoms are unusual.

The diagnosis is usually made clinically but a skin biopsy is sometimes used to help support the diagnosis. Interestingly, even experienced pathologists may under diagnose reaction in skin sections from patients with clinically apparent T1R.⁷ Important diagnostic features appear to be epithelioid cell granuloma oedema, dermal oedema, the presence of plasma cells and granuloma fraction. But standardised criteria for the histopathological diagnosis of T1Rs are needed.

Neuritis is present if an individual has any of the following: spontaneous nerve pain, paraesthesia, tenderness, or new sensory or motor impairment.⁸ Nerve pain, paraesthesia or tenderness may precede nerve function impairment (NFI), which, if not treated rapidly and adequately becomes permanent. NFI may arise in the absence of symptoms and may go unnoticed by the patient – ‘silent neuropathy’.

The detection of NFI is done clinically. Graded Semmes-Weinstein monofilaments (or a ball-point pen) are used to detect sensory loss. Voluntary muscle testing is used to assess motor nerve function. A recent study by van Brakel *et al.*, using nerve conduction studies and quantitative sensory testing, has demonstrated that individuals experiencing neuritis, NFI or reactional episodes either alone or in combination have evidence of sub-clinical neuropathy up to 12 weeks prior to clinically detectable changes.⁹ Individuals who have WHO disability grades 1 and 2 at diagnosis are significantly more likely to have severe T1Rs.¹⁰ T1Rs are frequently recurrent and this can lead to further nerve damage.¹¹ T1Rs can occur at any time but are frequently seen after starting multi-drug therapy (MDT) or during the puerperium.¹² Indian and Ethiopian cohort studies show that patients continue to experience reactions and neuropathy in the third year after diagnosis and beyond.^{9,13}

A retrospective study of 1,026 leprosy patients from Brazil found that a greater proportion of the 54 patients with HIV co-infection had BT leprosy compared with HIV negative leprosy patients. The HIV positive group had a significantly greater number of reactions (type not specified) at diagnosis than the HIV negative group but the cumulative rate of reactions in the two groups was similar overall.¹⁴

T1Rs have been increasingly reported in individuals with HIV co-infection as part of an immune reconstitution inflammatory syndrome following the commencement of anti-retroviral therapy.¹⁵ The influence of CD4 counts, viral load and anti-retroviral therapy on T1Rs and associated neuropathy requires investigation in well controlled studies.

PATHOPHYSIOLOGY AND IMMUNOLOGY OF TYPE 1 REACTIONS

T1Rs are delayed hypersensitivity reactions that occur predominantly in borderline forms of leprosy.¹⁶ *M. leprae* antigens have been demonstrated in the nerves and skin of patients experiencing T1Rs. The antigens were localised to Schwann cells and macrophages.¹⁷ A study of Brazilian patients with slit-skin smear negative single lesion paucibacillary leprosy showed that individuals with *M. leprae* DNA detectable by PCR in the skin were more likely to experience a T1R than those in whom *M. leprae* DNA was undetectable.¹⁸ Schwann cells express toll-like receptor (TLR) 2.¹⁹ *M. leprae* infection may lead to the expression of MHC II on the surface of the cells and this may give rise to antigen presentation which triggers CD4 lymphocyte killing of the cell mediated by cytokines such as TNF.²⁰

Ethiopian patients with a microsatellite polymorphism in the *tlr2* gene had an increased frequency of T1R. However, individuals with the single nucleotide polymorphism (SNP) 597C → T in the *tlr2* gene had a lower frequency of T1R.²¹ Having the SNP 1805T → G in the *tlr1* gene has been associated with a decreased risk of leprosy T1R in Nepali patients.²² This polymorphism appears to lead to a loss of expression of the receptor on the surface of peripheral blood monocytes.²³

More TNF protein is detectable using immunohistochemical techniques in the skin and nerves during T1Rs.²⁴ T1Rs appear to be mediated via Th1 type cells and lesions in reaction express the pro-inflammatory IFN- γ , IL-12 and the oxygen free radical producer inducible nitric oxide synthase.²⁵ The expression of mRNA of various chemokines including IL-8, monocyte chemoattractant protein 1 and RANTES is higher in the skin during reaction.²⁶

However, the levels of circulating cytokines do not reflect the local changes taking place in the skin during T1Rs. Treatment of the reaction causes clinical improvement but changes in the inflammatory cytokines lag behind by some considerable time and in some may remain unchanged.²⁷ A similar seemingly paradoxical finding has also been demonstrated in tuberculous meningitis.²⁸ This variation in the inflammatory activity within different compartments is important to bear in mind when designing experiments to study T1Rs and may help to explain why treatment is not always effective.

The inflammatory cytokines produced during a T1R may affect local conversion of endogenous corticosteroids (the cortisol-cortisone shuttle) in the lesional skin of leprosy patients with T1Rs.²⁹ The gene expression of the enzyme 11 β -hydroxysteroid dehydrogenase Type 2 which converts the active cortisol back to inactive cortisone is decreased in the skin of patients with T1R compared to non-reactional controls. This supports the hypothesis that local endogenous active steroid levels are increased during T1R in response to the marked inflammation that has been triggered but are insufficient to suppress it.

THE FREQUENCY OF TYPE 1 REACTIONS AND NEURITIS COMPLICATING LEPROSY

There have been relatively few epidemiological studies of T1Rs or neuritis in leprosy. Table 1 summarises some of the reports of the frequency of T1Rs.

The large variation in these rates is due to the different methodologies used and the changing definitions of paucibacillary and multibacillary categories.

30.1% of individuals with borderline leprosy in Nepal develop a T1R.¹¹ Half of these individuals have demonstrable new NFI. These figures are from a retrospective study conducted at a leprosy referral centre and similar studies conducted in India have reported T1R rates of 8.9% in a cohort from Hyderabad presenting in 1 year (1985) and followed for almost 6 years, 10.7% in Orissa between 1992 and 2002 and 24.1% in Chandigarh over 15 years.^{6,30,31} The cumulative rate in Hyderabad was 24% for 'paucibacillary' (tuberculoid and borderline tuberculoid) patients in the 5 year period 1982 to 1987.³² 19.8% (60 of 303) of the ILEP Nerve Function Impairment and Reaction (INFIR) cohort had a T1R at recruitment.⁸ Thirty nine per cent (74 of 188) experienced a reaction or NFI during the 2 year follow up period. A T1R occurred in 10% (19 of 188) of individuals during the study period.⁹ The 12 individuals who were diagnosed with a T1R limited to the skin had demonstrable sub-clinical nerve involvement using sensory nerve conduction and/or warm detection thresholds (P. Nicholls, personal communication).

35.7% of a cohort of 'MB' patients in Malawi experienced a T1R or a deficit in nerve function;³³ 19.9% of individuals enrolled in a prospective study from a referral centre in Thailand developed a T1R, each patient was followed for a minimum of 3 years after being diagnosed with leprosy.³⁴ A prospective hospital based study from Vietnam demonstrated a prevalence of T1Rs of 29.1% in 237 patients.¹ A retrospective study conducted in the field in Bangladesh identified T1Rs in 8.8% of individuals.³⁵ A prospective study in Bangladesh with 5 years follow up demonstrated an incidence of T1Rs of 17% in MB patients.³⁶ A prospective field study of 594 individuals with up to 10 years follow up from Ethiopia reported a rate of T1Rs of 16.5%.¹³ The prospective study from Bangladesh suggests that nerve function impairment and T1Rs occur more than 1.7 times more frequently in men than women.³⁷ This finding needs further confirmation in other studies.

STUDIES OF TYPE 1 REACTIONS AND NEURITIS TREATED WITH CORTICOSTEROIDS

There were few good data for making evidence-based treatment decisions about managing T1Rs or NFI. This was highlighted by the Cochrane systematic review 'Corticosteroids for treating nerve damage in leprosy' by van Veen *et al.*³⁸ Three randomised controlled trials were included in the review. The sole trial which examined the effect of corticosteroids in T1R did not fulfil the initial inclusion criteria of the review.

Table 2 summarises the published studies of prospective cohorts in which systemic corticosteroids or other immunosuppressants were used to treat T1Rs and/or nerve involvement due to leprosy. Studies that were not formal clinical trials were included if there was a clearly stated clinical outcome. There are only four randomised studies all of which were conducted in south Asia.

Table 1. The frequency of Type 1 reactions

Location of study	Type of study	Number of patients	Type of leprosy	Duration of follow up (years)	Frequency of Type 1 reactions and/or nerve function impairment (%)
PROSPECTIVE STUDIES					
Ethiopia ¹³	Cohort study	594	New patients	6–11	16.5
Bangladesh ³⁶	Cohort study	2664	Paucibacillary (PB) and Multibacillary (MB)	PB 3 MB 5	PB 0.9 MB 17
Naini and Faizabad, India ⁸	Cohort study	303	Multibacillary	2	19.8
Thailand ³⁴	Cohort study	176	All newly diagnosed types	3 minimum	19.9
Vietnam ¹	Case–control study	237	All types except indeterminate	Not clear	29.1
Malawi* ³³	Randomized trial of MB MDT	305	Multibacillary BI \geq 2 at any site	Mean follow up 3 years	35.7
RETROSPECTIVE STUDIES					
Hyderabad, India ³⁰	Leprosy research centre clinic records review	494	All types	\leq 6	8.9
Orissa, India ³¹	Regional leprosy centre records review	942	Patients registered between 1992–2002	Not clear	10.7
Hyderabad, India* ³²	Leprosy research centre clinic records review	1226	Paucibacillary (Tuberculoid and borderline tuberculoid 1982–87)	Not clear	24
Chandigarh, India ⁶	Tertiary referral clinic records review	2867	All types except pure neuritic leprosy	3–13	24.1 at presentation. 33 overall
Brazil ⁶⁶	Leprosy clinic records review	162	Untreated slit skin smear positive patients	Not clear	25.9
Nepal ¹¹	Leprosy hospital clinic records review	386	Untreated patients except those with pure neuritic leprosy	Mean 1.73	30.1

* These studies used definitions of PB and MB leprosy which differ from the current WHO definitions.

Table 2. Prospective studies using steroids in Type 1 reactions and/or nerve function impairment.

Author, Year, Country	Type of study	Entry criteria	Number enrolled	Intervention	Outcome measures	Conclusion
Marlowe, 2007, Ethiopia, Nepal ⁵⁴	Open, uncontrolled	Severe acute Type 1 reactions	43	12 weeks ciclosporin 5 mg/kg and prednisolone 40 mg for first 5 days Ciclosporin increased to 7.5 mg/kg if deterioration	Skin and nerve score Improvement in clinical outcomes and relapse	Variable improvement in skin and nerve signs High levels of recurrence of reaction particularly in Ethiopian patients
Rao, 2006, India ⁴⁶	Double-blind randomised controlled, parallel group	'Severe' Type 1 reactions	334	3 prednisolone regimes: 3.5 g over 5 months 2.31 g over 5 months 2.94 g over 3 months	Amount of extra prednisolone required	The 5 month regimes were equally effective and less additional prednisolone was required by these two groups than by the 3 month group Equally effective
Marlowe, 2004, Nepal ⁵³	Randomised, controlled	Type 1 reactions skin or skin and nerve	40	12 weeks azathioprine and 8 weeks prednisolone compared to 12 weeks prednisolone alone	Skin signs, nerve tenderness, sensory and motor testing and amount of extra prednisolone required	Equally effective
Richardus, 2003, Nepal, Bangladesh ⁵⁰	Randomised placebo controlled, double blind	NFI of 6–24 months duration	92	16 week standard prednisolone regime	Sensory and motor test scores	No difference
van Brakel, 2003, Nepal, Bangladesh ⁶⁷	Randomized placebo controlled, double blind	Isolated mild sensory impairment	75	16 week standard prednisolone regime	Improvement in monofilament scores	No difference between treated and untreated groups
Saunderson, 2000, Ethiopia ²	Prospective field observation study	Neuropathy including nerve tenderness	594	Steroid regimes for PB (12 weeks) and MB (24 weeks) patients	Motor and sensory testing and symptom improvement	73% of all neuropathy given steroids responded fully in 73 patients with no impairment at diagnosis
Croft, 2000, Bangladesh ³	Prospective, open, uncontrolled	NFI	132	16 week standard prednisolone regime	Improvement	33% of motor nerves and 37% of sensory nerves fully recovered at 12 months 67% of nerves improved

Table 2. *continued*

Author, Year, Country	Type of study	Entry criteria	Number enrolled	Intervention	Outcome measures	Conclusion
Schreuder, 1998, Thailand ⁴⁰	Observation study	Newly diagnosed leprosy patients	640	Not clear	Nerve function	Nerve damage at presentation improves in only 44% compared to 82% improvement in damage developing whilst on treatment
Wilder-Smith, 1997, Nepal ⁶⁸	Prospective	Skin signs – obligatory Nerve signs – optional Oedema/Fever – optional	18	Prednisolone starting at 40 mg and tapered according to individual response	Nerve function	21.2% improved sensory function and 1.3% improved motor function
Kiran, 1985, India ⁶⁹	?Prospective Open, uncontrolled	Impaired VMT or ST	33	Semi-standardised prednisolone regime	Nerve score	Good result in 74% of nerves
Touw-Langendijk, 1984, Ethiopia ⁷⁰	Open, uncontrolled	Recent nerve function loss	36	6 month course of prednisolone	Sensory and motor function	63% of affected nerves (59/93) 'improved'

Table 3. Retrospective reports of steroids in Type 1 reactions and/or nerve function impairment*

Author, Year, Country	Type of study	Criteria for review	Number analysed	Measures	Conclusion
Santaram, 2004, India ³¹	Retrospective	All reactions	101 Type 1 reactions of 942 cases	'Satisfactory response'	95.2% of all reactions had satisfactory response
Bernink, 1997, Indonesia ⁷¹	Retrospective field study	Nerve function impairment in all types of reaction	154	Improvement, the same or worse	75% of nerves improved in all types of reaction
van Brakel, 1996, Nepal ⁴⁹	Retrospective	Nerve function impairment	168	Comparison of nerve function at 3 and 6 months after steroids	Up to 47% showed no functional improvement
Lockwood, 1993, India ³⁰	Retrospective review of all cases from 1985	Type 1 reaction	44 Type 1 reaction of 494 cases	Improvement in symptoms and signs	93% of skin lesions and 50% of neuritic episodes responded
Becx-Bleumink, 1992, Ethiopia ⁷²	Retrospective review of all reactions	All reactions	365 Type 1 reactions	Recurrent reaction	Approx a third of BL patients relapse as steroids cut. 25% of nerves do not improve
Kiran, 1991, India ⁷³	Retrospective	≤6 months of facial nerve damage with lagophthalmos	27 (36 eyes)	Nerve function loss Degree of eyelid lag in mm	64% had a good response
Naafs, 1979, Ethiopia ⁷⁴	Retrospective review of reaction and neuritis	Neuritis of selected patients	48	VMT deficit	A longer course is better than a short one

* Checklist for patients starting high dose corticosteroids: Monitor blood pressure and weight at each visit; Urinalysis or blood glucose estimation; Gastric protection with H2 blocker or proton pump inhibitor; Treat those at risk of *Strongyloides stercoralis* with albendazole or ivermectin; Osteoporosis prevention.

Table 3 summarises reports of retrospective studies of the effect of corticosteroids on T1Rs and/or nerve function impairment in patient series from Ethiopia, India, Nepal and Indonesia.

Only limited conclusions can be drawn from these series. These studies suggest more favourable responses to corticosteroids than the prospective data from the more rigorous studies in Table 2. Despite this they clearly indicate a less than satisfactory response of T1Rs or isolated nerve function impairment to corticosteroids.

Different methodologies employing different entry criteria and outcome measures have made it difficult to compare studies. The grouping together of all individuals with T1R regardless of whether new NFI is a feature of the reaction makes it difficult to assess the impact on nerve function of the treatments being studied. The difficulty in recruiting sufficient numbers of patients is a logistical problem that is best addressed using large multi-centre studies.

The development of a clinical scale to measure the severity of reactions has been undertaken.³⁹ A clinical severity scale based on the scales used in the INFIR studies has been validated in Bangladesh and Brazil (Walker *et al.* PLoS Negl Trop Dis *in press*). This measurement tool will facilitate the comparison of subjects enrolled in a study and the outcomes between studies. Further work is required to determine how useful a validated scale is in reflecting response to treatment.

Studies have also used different features of nerve involvement such as nerve function impairment and neuritis as entry criteria and outcome measures. Another difficulty has been in trying to compare studies that use improvement as an outcome with those that use the more stringent criterion of recovery. Some published studies have even looked at T1Rs and erythema nodosum leprosum (Type 2 reactions) together despite their different aetiology, clinical presentation and response to treatment.

Several studies have indicated that some nerve function impairment will improve without steroid therapy. This improvement may be spontaneous or attributable to MDT.^{2,3,40} The prospective BANDS cohort included 69 individuals with NFI who should have received prednisolone but did not. In these patients 33% of involved motor nerves and 62% of sensory nerves had some degree of improvement at 12 months follow up.³ The AMFES cohort included 141 individuals with NFI at the time of enrolment which had been present for longer than 6 months and so were not treated with steroids. Between a quarter and a third of nerves with this longstanding impairment fully improved during the long period of follow up.²

The effective killing of *M. leprae* by MDT may improve neuropathy which is due to direct bacillary invasion of nerves and allow some axonal regeneration. The phenomenon of spontaneous improvement in nerve function is another confounder in determining the size of the effect of any intervention being studied. It would now be unethical to conduct a trial of the effect of steroids compared to inactive placebo.

Women are under represented in the studies of T1Rs. The under representation of certain groups affects many clinical trials worldwide.⁴¹ The results of trials may not be applicable if the study population is not representative. The lack of recruitment of women is a cause for concern. Gender inequalities may be more significant in leprosy as it is a highly stigmatising disease.⁴² All the prospective studies outlined in Table 2 have recruited more men than women with rates of female recruitment varying from 13–36%. Furthermore during the puerperium it is very difficult to enrol women into trials.

TREATMENT OF TYPE 1 REACTIONS

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. The use of adrenocorticotrophic hormone in the management of leprosy reactions was first reported by Roche *et al.* in 1951.⁴³

Corticosteroids bind to specific glucocorticoid receptors (GR) in the cytoplasm of the cell. Once in the nucleus the GR-steroid complexes form dimers and bind to the promoter region of steroid responsive genes known as glucocorticoid response elements (GRE). Activation of GRE leads to the transcription of genes encoding anti-inflammatory mediators such as annexin-1, MAP kinase phosphatase-1, I- κ B α , secretory leukocyte protease inhibitor and glucocorticoid-induced leucine zipper.^{44,45} Activated GR-steroid complexes may also interact with the coactivator molecule and transcription factor complexes in the nucleus. This reduces the production of proinflammatory cytokines. Corticosteroids, particularly in higher concentrations, exert genomic effects (binding via the GR to DNA). They also have nongenomic effects such as inhibiting transcription factors and destabilising mRNA.

Individuals with inflamed skin plaques, neuritis or nerve function impairment are treated with oral corticosteroids. Different regimes have been employed in the management of T1Rs. The practice at the Hospital for Tropical Diseases in London is to use a starting dose of 30–40 mg of prednisolone tapered to zero over a period of 5–6 months. A randomised study of three different prednisolone regimes suggested that duration of treatment, rather than the starting dose of prednisolone, may be more important in controlling T1Rs.⁴⁶ Prednisolone 30 mg tapered slowly to zero over 20 weeks was superior to prednisolone 60 mg tapered over 12 weeks. Individuals with and without nerve involvement were enrolled into the study. 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.

The role of a 4 month course of prophylactic steroids in the prevention of reactional episodes, neuritis and nerve function impairment has been studied. The prednisolone had a protective effect whilst patients were taking it but at 12 month follow up this effect had been lost.⁴⁷ The current WHO document: 'The Global Strategy for Further Reducing the Leprosy Burden and Sustaining Leprosy Control Activities (2006–2010)' states that 'Severe reversal reactions should be treated with a course of steroids, usually lasting 3–6 months'.⁴⁸ Only 60% of individuals will show improvement in nerve function with 12 weeks of oral prednisolone.⁴⁹ Skin lesions will readily respond. The Global Strategy also states that reactions requiring steroids should be referred to a specialist unit.

There is a consensus amongst leprologists that the use of steroids in nerve function impairment is not worthwhile if the impairment has been present for more than 6 months. This view is supported by the TRIPOD 3 study⁵⁰ which did not demonstrate any significant improvement of nerve function present for longer than 6 months with prednisolone compared to placebo.

A trial in which individuals with ulnar neuritis were randomised to either 6 weeks prednisolone or medial epicondylectomy and 6 weeks prednisolone demonstrated improvement in nerve function in both groups but did not show any added benefit of surgery.⁵¹ A study from Senegal in 31 patients with neuritis who were treated with prednisone for 6 months did not demonstrate any additional benefit of early surgery in those nerves randomised to receive a decompression procedure and epineurotomy.⁵²

Azathioprine in combination with an 8 week course of prednisolone was as effective as a 12 week course of prednisolone in the management of T1Rs in a pilot study in Nepal.⁵³ Ciclosporin has been used in pilot studies in Nepal and Ethiopia with some success.⁵⁴

There is no evidence to guide physicians in the optimal use of immunosuppression to manage T1Rs affecting HIV positive individuals. A Ugandan study of patients with T1Rs reported a similar response to steroids in the HIV infected and non-infected groups.⁵⁵ The current treatment of T1Rs in HIV infected individuals is with corticosteroids just as in uninfected patients. The reported cases of T1Rs in co-infected individuals, whether ART related or not, have all used corticosteroids. One individual required the introduction of azathioprine to control repeated relapses of his steroid dependent T1R.⁵⁶

An international workshop on neuropathology in leprosy produced a consensus report which outlines research priorities in improving the understanding and management of nerve damage. Many of these are relevant to T1Rs including the identification of markers of reaction, large randomised controlled trials of corticosteroids (including patient tailored regimens), alternative drug treatments and surgery.⁵⁷ (Figure 1)

Monitor blood pressure and weight at each visit Urinalysis or blood glucose estimation Gastric protection with H2 blocker or proton pump inhibitor Treat those at risk of <i>Strongyloides stercoralis</i> with albendazole or ivermectin Osteoporosis prevention

Figure 1. Checklist for patients starting high dose corticosteroids.

CONCERNS ABOUT THE USE OF CORTICOSTEROIDS

The risks associated with the administration of any drug are a concern. The use of potent immunosuppressants is potentially problematic in areas endemic for severe infections such as tuberculosis. Immunosuppression may also make infective conditions such as strongyloidiasis worse.⁵⁸ The First European Workshop on Glucocorticoid Therapy designated doses of prednisone between > 30 mg and ≤ 100 mg as 'high doses' which are associated with severe side effects if used long term. This group also considers that side effects are considerable and dose dependent at 'medium doses' of between > 7.5 mg and ≤ 30 mg.⁵⁹

There is little evidence concerning the long term sequelae of corticosteroids used to treat patients with T1Rs. Corticosteroids cause bone demineralisation leading to osteoporosis. This is a dose dependent phenomenon and the rate of loss of bone mineral density is considerable in the first 6 months of steroid therapy.⁶⁰ Men with leprosy are at increased risk of osteoporosis and this is associated with hypogonadism.⁶¹ The role of previous corticosteroid therapy in exacerbating the osteoporosis affecting people who have had leprosy has not been assessed. Osteoporosis may become increasingly important if longer courses of steroids are conclusively proven to be superior in the management of T1Rs. At the Hospital for Tropical Diseases patients taking prednisolone for T1Rs are also prescribed calcium carbonate and cholecalciferol which they take until they no longer require corticosteroids. Studies are required to assess both the extent of bone demineralisation in leprosy patients treated with steroids and interventions that mitigate it.

Diabetes and hyperglycaemia may occur during treatment with low doses of corticosteroids. A case-controlled study of patients in a Medicaid programme in the USA showed that at low steroid doses hypoglycaemic agents may be required.⁶² In a large series of 581 Indian patients with T1R, 2.2% developed diabetes requiring an oral hypoglycaemic agent during the initial phase of treatment with corticosteroids.⁶³ Cataracts are associated with corticosteroid use but may also complicate leprosy (particularly MB disease) *per se*. Cataract was identified in 4% of individuals treated for T1R by Sugumaran but all of these patients had been on steroids for more than 12 months.⁶³ Age-related cataract is now the commonest cause of blindness in leprosy affected people.⁶⁴

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 regimens.⁶⁵ The trials used a total prednisolone dose of 1.96 g and 2.52 g. 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 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.

Conclusion

Systemic corticosteroids are the mainstay of treatment of T1Rs although conclusive evidence of their efficacy is lacking. The optimal dose and duration of treatment with steroids is still unclear although there is evidence that suggests prolonged therapy improves outcome. The controlled trial that gives most weight to this argument did not use nerve function as an outcome measure.

There is no evidence about the degree of benefit attributable to corticosteroids or the degree of nerve damage that will respond. There is a real need for large trials to identify the optimal steroid regime in T1Rs. These studies need to be well controlled and representative.

The role of other drugs in the management of reactions and nerve function impairment also needs to be investigated. The optimal use of these either alone or in conjunction with corticosteroids needs to be more clearly defined.

The role of surgery in the management of NFI needs to be better defined, and further investigation of sub-clinical changes in nerve function prior to and during T1R is warranted.

Conflict of interests

None, and neither of the authors were involved in the editorial process for this manuscript, which was edited by Professor Anthony Bryceson.

Acknowledgements

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 Ranque B, Nguyen VT, Vu HT *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.
- ² Saunderson P, Gebre S, Desta K *et al.* The pattern of leprosy-related neuropathy in the AMFES patients in Ethiopia: definitions, incidence, risk factors and outcome. *Lepr Rev*, 2000; **71**: 285–308.
- ³ Croft RP, Nicholls PG, Richardus JH, Smith WC. The treatment of acute nerve function impairment in leprosy: results from a prospective cohort study in Bangladesh. *Lepr Rev*, 2000; **71**: 154–168.
- ⁴ Ridley DS, Jopling WH. Classification of leprosy according to immunity. *Int J Lepr Other Mycobact Dis*, 1966; **34**: 255–273.
- ⁵ Modlin RL, Melancon-Kaplan J, Young SM *et al.* Learning from lesions: patterns of tissue inflammation in leprosy. *Proc Natl Acad Sci USA*, 1988; **85**: 1213–1217.
- ⁶ 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**: 125–133.
- ⁷ Lockwood DN, Lucas SB, Desikan K, *et al.* The histological diagnosis of leprosy Type 1 reactions: identification of key variables and an analysis of the process of histological diagnosis. *J Clin Pathol*, 2008 March 6.
- ⁸ van Brakel WH, Nicholls PG, Das L *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.
- ⁹ van Brakel WH, Nicholls PG, Wilder-Smith EP *et al.* Early Diagnosis of Neuropathy in Leprosy-Comparing Diagnostic Tests in a Large Prospective Study (the INFIR Cohort Study). *PLoS Negl Trop Dis*, 2008; **2**: e212.
- ¹⁰ 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, 1998; **66**: 159–169.
- ¹¹ 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.
- ¹² Lockwood DN, Sinha HH. Pregnancy and leprosy: a comprehensive literature review. *Int J Lepr Other Mycobact Dis*, 1999; **67**: 6–12.
- ¹³ Saunderson P, Gebre S, Byass P. Reversal reactions in the skin lesions of AMFES patients: incidence and risk factors. *Lepr Rev*, 2000; **71**: 309–317.
- ¹⁴ Sarno EN, Illarramendi X, Nery JA *et al.* HIV-M. *leprae* interaction: can HAART modify the course of leprosy? *Public Health Rep*, 2008; **123**: 206–212.
- ¹⁵ Deps PD, Lockwood DN. Leprosy occurring as immune reconstitution syndrome. *Trans R Soc Trop Med Hyg*, 2008; **102**: 966–968.
- ¹⁶ Job CK. Pathology of leprosy. In: Hastings RC (ed). *Leprosy*, 2nd edn. Churchill Livingstone, Edinburgh, 1994; pp. 193–234.
- ¹⁷ 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**: 409–415.
- ¹⁸ Sousa AL, Stefani MM, Pereira GA *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**: 829–833.
- ¹⁹ Oliveira RB, Ochoa MT, Sieling PA *et al.* Expression of Toll-like receptor 2 on human Schwann cells: a mechanism of nerve damage in leprosy. *Infect Immun*, 2003; **71**: 1427–1433.
- ²⁰ Ochoa MT, Stenger S, Sieling PA *et al.* T-cell release of granulysin contributes to host defense in leprosy. *Nat Med*, 2001; **7**: 174–179.
- ²¹ Bochud PY, Hawn TR, Siddiqui MR *et al.* Toll-like receptor 2 (TLR2) polymorphisms are associated with reversal reaction in leprosy. *J Infect Dis*, 2008; **197**: 253–261.
- ²² Misch EA, Macdonald M, Ranjit C *et al.* Human TLR1 Deficiency Is Associated with Impaired Mycobacterial Signaling and Protection from Leprosy Reversal Reaction. *PLoS Negl Trop Dis*, 2008; **2**: e231.
- ²³ Johnson CM, Lyle EA, Omueti KO *et al.* Cutting edge: a common polymorphism impairs cell surface trafficking and functional responses of TLR1 but protects against leprosy. *J Immunol*, 2007; **178**: 7520–7524.
- ²⁴ Khanolkar-Young S, Rayment N, Brickell PM *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.
- ²⁵ Little D, Khanolkar-Young S, Coulthart A *et al.* 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**: 3413–3417.
- ²⁶ Kirkaldy AA, Musonda AC, Khanolkar-Young S *et al.* Expression of CC and CXC chemokines and chemokine receptors in human leprosy skin lesions. *Clin Exp Immunol*, 2003; **134**: 447–453.

- ²⁷ Andersson AK, Chaduvula M, Atkinson SE *et al.* Effects of prednisolone treatment on cytokine expression in patients with leprosy type 1 reactions. *Infect Immun*, 2005; **73**: 3725–3733.
- ²⁸ Simmons CP, Thwaites GE, Quyen NT *et al.* The clinical benefit of adjunctive dexamethasone in tuberculous meningitis is not associated with measurable attenuation of peripheral or local immune responses. *J Immunol*, 2005; **175**: 579–590.
- ²⁹ Andersson AK, Atkinson SE, Khanolkar-Young S *et al.* Alteration of the cortisol-cortisone shuttle in leprosy type 1 reactions in leprosy patients in Hyderabad, India. *Immunol Lett*, 2007; **109**: 72–75.
- ³⁰ Lockwood DN, Vinayakumar S, Stanley JN *et al.* Clinical features and outcome of reversal (type 1) reactions in Hyderabad, India. *Int J Lepr Other Mycobact Dis*, 1993; **61**: 8–15.
- ³¹ Santaram V, Porichha D. Reaction cases treated at the Regional Leprosy Training and Research Institute, Aska, Orissa: a retrospective analysis. *Indian J Lepr*, 2004; **76**: 310–320.
- ³² Hogeweg M, Kiran KU, Suneetha S. The significance of facial patches and type I reaction for the development of facial nerve damage in leprosy. A retrospective study among 1226 paucibacillary leprosy patients. *Lepr Rev*, 1991; **62**: 143–149.
- ³³ Ponnighaus JM, Boerrigter G. Are 18 doses of WHO/MDT sufficient for multibacillary leprosy; results of a trial in Malawi. *Int J Lepr Other Mycobact Dis*, 1995; **63**: 1–7.
- ³⁴ Scollard DM, Smith T, Bhoopat L *et al.* Epidemiologic characteristics of leprosy reactions. *Int J Lepr Other Mycobact Dis*, 1994; **62**: 559–567.
- ³⁵ Richardus JH, Finlay KM, Croft RP, Smith WC. Nerve function impairment in leprosy at diagnosis and at completion of MDT: a retrospective cohort study of 786 patients in Bangladesh. *Lepr Rev*, 1996; **67**: 297–305.
- ³⁶ Richardus JH, Nicholls PG, Croft RP *et al.* Incidence of acute nerve function impairment and reactions in leprosy: a prospective cohort analysis after 5 years of follow-up. *Int J Epidemiol*, 2004; **33**: 337–343.
- ³⁷ Croft RP, Nicholls PG, Richardus JH, Smith WC. Incidence rates of acute nerve function impairment in leprosy: a prospective cohort analysis after 24 months (The Bangladesh Acute Nerve Damage Study). *Lepr Rev*, 2000; **71**: 18–33.
- ³⁸ Van Veen NH, Nicholls PG, Smith WC, Richardus JH. Corticosteroids for treating nerve damage in leprosy. *Cochrane Database Syst Rev*, 2007; CD005491.
- ³⁹ Van Brakel WH, Nicholls PG, Lockwood DN *et al.* A scale to assess the severity of leprosy reactions. *Lepr Rev*, 2007; **78**: 161–164.
- ⁴⁰ 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]. III. Neural and other impairments. *Int J Lepr Other Mycobact Dis*, 1998; **66**: 170–181.
- ⁴¹ Bolen S, Tilburt J, Baffi C *et al.* Defining ‘success’ in recruitment of underrepresented populations to cancer clinical trials: moving toward a more consistent approach. *Cancer*, 2006; **106**: 1197–1204.
- ⁴² Le Grand A. Women and leprosy: a review. *Lepr Rev*, 1997; **68**: 203–211.
- ⁴³ Roche M, Convit J, Medina JA, Blomenfeld E. The effects of adrenocorticotrophic hormone (ACTH) in lepromatous lepra reaction. *Int J Lepr*, 1951; **19**: 137–145.
- ⁴⁴ Perretti M, D’Acquisto F. Novel aspects of annexin 1 and glucocorticoid biology: intersection with nitric oxide and the lipoxin receptor. *Inflamm Allergy Drug Targets*, 2006; **5**: 107–114.
- ⁴⁵ Barnes PJ. How corticosteroids control inflammation: Quintiles Prize Lecture 2005. *Br J Pharmacol*, 2006; **148**: 245–254.
- ⁴⁶ 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.
- ⁴⁷ Smith WC, Anderson AM, Withington SG *et al.* Steroid prophylaxis for prevention of nerve function impairment in leprosy: randomised placebo controlled trial (TRIPOD 1). *BMJ*, 2004; **328**(7454): 1459.
- ⁴⁸ <http://www.who.int/lep/resources/SEAGLP20062.pdf> was accessed on 30.11.2008
- ⁴⁹ 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**: 104–118.
- ⁵⁰ Richardus JH, Withington SG, Anderson AM *et al.* Treatment with corticosteroids of long-standing nerve function impairment in leprosy: a randomized controlled trial (TRIPOD 3). *Lepr Rev*, 2003; **74**: 311–318.
- ⁵¹ Pannikar VK, Ramprasad S, Reddy NR *et al.* Effect of epicondylectomy in early ulnar neuritis treated with steroids. *Int J Lepr Other Mycobact Dis*, 1984; **52**: 501–505.
- ⁵² Boucher P, Millan J, Parent M, Moulia-Pela JP. Randomized controlled trial of medical and medico-surgical treatment of Hansen’s neuritis. *Acta Leprol*, 1999; **11**: 171–177.
- ⁵³ Marlowe SN, Hawksworth RA, Butlin CR *et al.* 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**: 602–609.
- ⁵⁴ Marlowe SN, Leekassa R, Bizuneh E *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**: 1004–1012.
- ⁵⁵ 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**: 315–316.

- ⁵⁶ 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–e6.
- ⁵⁷ Van Brakel WH, Saunderson P, Shetty V *et al*. International workshop on neuropathology in leprosy-consensus report. *Lepr Rev*, 2007; **78**: 416–433.
- ⁵⁸ Leang B, Lynen L, Tootill R *et al*. Death caused by strongyloides hyperinfection in a leprosy patient on treatment for a type II leprosy reaction. *Lepr Rev*, 2004; **75**: 398–403.
- ⁵⁹ Buttgereit F, da Silva JA, Boers M *et al*. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Ann Rheum Dis*, 2002; **61**: 718–722.
- ⁶⁰ <http://www.rcplondon.ac.uk/pubs/books/glucocorticoid/Glucocorticoid.pdf> was accessed on 30.11.2008
- ⁶¹ Ishikawa S, Ishikawa A, Yoh K *et al*. Osteoporosis in male and female leprosy patients. *Calcif Tissue Int*, 1999; **64**: 144–147.
- ⁶² Gurwitz JH, Bohn RL, Glynn RJ *et al*. Glucocorticoids and the risk for initiation of hypoglycemic therapy. *Arch Intern Med*, 1994; **154**: 97–101.
- ⁶³ Sugumaran DS. Leprosy reactions—complications of steroid therapy. *Int J Lepr Other Mycobact Dis*, 1998; **66**: 10–15.
- ⁶⁴ Hogeweg M, Keunen JE. Prevention of blindness in leprosy and the role of the Vision Programme. *Eye*, 2020; **19**: 1099–1105.
- ⁶⁵ Richardus JH, Withington SG, Anderson AM *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**: 319–327.
- ⁶⁶ Nery JA, Vieira LM, de Matos HJ *et al*. Reactional states in multibacillary Hansen disease patients during multidrug therapy. *Rev Inst Med Trop Sao Paulo*, 1998; **40**: 363–370.
- ⁶⁷ Van Brakel WH, Anderson AM, Withington SG, *et al*. The prognostic importance of detecting mild sensory impairment in leprosy: a randomized controlled trial (TRIPOD 2). *Lepr Rev*, 2003; **74**: 300–310.
- ⁶⁸ Wilder-Smith A, Wilder-Smith E. Effect of steroid therapy on parameters of peripheral autonomic dysfunction in leprosy patients with acute neuritis. *Int J Lepr Other Mycobact Dis*, 1997; **65**: 20–27.
- ⁶⁹ Kiran KU, Stanley JN, Pearson JM. The outpatient treatment of nerve damage in patients with borderline leprosy using a semi-standardized steroid regimen. *Lepr Rev*, 1985; **56**: 127–134.
- ⁷⁰ Touw-Langendijk EM, Brandsma JW, Andersen JG. Treatment of ulnar and median nerve function loss in borderline leprosy. *Lepr Rev*, 1984; **55**: 41–46.
- ⁷¹ Bernink EH, Voskens JE. Study on the detection of leprosy reactions and the effect of prednisone on various nerves, Indonesia. *Lepr Rev*, 1997; **68**: 225–232.
- ⁷² 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**: 173–184.
- ⁷³ Kiran KU, Hogeweg M, Suneetha S. Treatment of recent facial nerve damage with lagophthalmos, using a semistandardized steroid regimen. *Lepr Rev*, 1991; **62**: 150–154.
- ⁷⁴ Naafs B, Pearson JM, Wheate HW. Reversal reaction: the prevention of permanent nerve damage. Comparison of short and long-term steroid treatment. *Int J Lepr Other Mycobact Dis*, 1979; **47**: 7–12.