LEPROSY REACTIONS

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Introduction

Leprosy reactions are inflammatory episodes that complicate the course of a *Mycobacterium leprae* infection. Leprosy reactions are immunological responses to *M. leprae* antigen. Other mycobacterial diseases such as tuberculosis (1), *Mycobacterium ulcerans* Disease (2), and, occasionally, non-tuberculous mycobacterial infections (3) are also associated with inflammatory episodes. However, the latter are often related to antimicrobial therapy and do not occur as frequently as leprosy reactions. Leprosy reactions can cause peripheral nerve damage, thereby contributing to disability. The early recognition of reactions is important for minimizing nerve damage.

Reactions place a significant burden on leprosy services. Leprosy reactions may occur before, during, or after the successful completion of multi-drug therapy (MDT). The timing of the reactions has implications for the clinical diagnosis of leprosy, adherence to MDT, and determination of relapse or re-infection. Leprosy reactions require treatment with immunomodulatory drugs, high doses of which are often required over prolonged periods and may contribute to morbidity. Healthcare workers dealing with patients who have leprosy reactions need to be trained in the recognition and management of the complications of immunosuppression. Similarly, physicians must be aware of potential interactions between the drugs used to treat the reactions and the components of MDT.

Two distinct types of leprosy reaction can occur: Leprosy Type 1 reactions (T1Rs), also known as reversal reactions, and Type 2 reactions (T2Rs), also known as erythema nodosum leprosum (ENL). Some leprologists reserve the term ENL for the skin lesions associated with the systemic illness of T2R; however, in this chapter, the term ENL will be used to refer to the whole syndrome. There are no data that suggest any difference in the incidence or clinical course of leprosy reac-

tions in patients with leprosy caused by *Mycobacterium leprae* or *M. lepromatosis* or in those with molecular evidence of a dual infection (4, 5) (see Chapter 8.2).

The distinct risk factors, pathogenesis, clinical features, and responses to treatment of T1R and ENL reactions means that they are best dealt with separately, as shown in the sections below. Another complication of leprosy, Lucio's Phenomenon, is often referred to as a third type of leprosy reaction. Lucio's Phenomenon is best viewed as a vasculopathy rather than an immunologically mediated inflammatory reaction; however, it is also covered in this chapter.

Leprosy Type 1 Reactions

EPIDEMIOLOGY

Reports of the proportion of individuals who experience T1Rs are highly variable depending on the type of study and the setting in which it was performed. Prospective studies suggest that the proportion of individuals with multibacillary (MB) leprosy who experience a T1R is between 20–40% (6, 7, 8, 9, 10, 11). A study performed in Brazil, Nepal, and the Philippines reported that 13.7% of patients with leprosy had a T1R at diagnosis (12). The cumulative incidence of T1R in patients with paucibacillary (PB) leprosy in Bangladesh was only 0.9% (13).

The borderline forms of leprosy pose a strong risk factor for the occurrence of T1Rs (8), although a small number of patients with the polar forms of leprosy may also experience them (14). In the INFIR cohort study, sixty-nine (36.7%) of the 188 MB participants who did not have a reaction or nerve function impairment (NFI) at baseline experienced a T1R during the two year follow-up period (7). In the same study, abnormal sensory nerve conduction in the ulnar and radial cutaneous nerves at baseline was predictive of a future T1R.

Older patients (≥ 15 years) may be at greater risk of experiencing T1R than children with leprosy (8). Individuals who have WHO disability grades 1 or 2 at diagnosis are also significantly more likely to have severe T1Rs (15). T1Rs can occur at any time but are frequently seen after starting MDT or during the puerperium (16).

Borderline patients with positive slit-skin smears are more likely to experience a T1R (17). A study of Brazilian patients with slit-skin smear negative single-lesion PB 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). Finally, individuals with borderline forms of leprosy who are seropositive for anti-PGL-1 antibodies also have an increased risk of T1R (19).

PATHOGENESIS

T1Rs are delayed hypersensitivity reactions that predominantly occur in borderline forms of leprosy (20). *M. leprae* antigens, localized in the Schwann cells, which express TLR2, and macrophages, have been found in the nerves and skin of patients experiencing T1Rs (21), (22). An *M. leprae* infection may lead to the expression of MHC II on the surface of the cells, potentially giving rise to an antigen presentation that triggers CD4 lymphocyte killing of the infected cell. The destruction of the infected cell is mediated by cytokines such as TNFα (23), as shown in a study that detected increased TNFα protein in the skin and nerves of 14 patients during T1Rs (24). Single nucleotide polymorphisms (SNPs) in the *TNFSF15-TNFSF8* locus are risk factors for T1R (25), but, interestingly, their effects may vary with age (26). The same group has also identified a missense *LRRK2* variant, which likely results in a pro-inflammatory mechanism, that is associated with T1R (27). This finding supports the hypothesis that the reaction has an inflammatory pathway in common with Crohn's disease.

T1Rs appear to be mediated via Th1 type cells. Lesions in the reaction express pro-inflammatory IFNγ, IL12, and the oxygen-free radical producer iNOS (28). Stefani and colleagues recently showed that 10 smear-negative newly diagnosed borderline tuberculoid (BT) patients with T1Rs had significantly elevated levels of plasma CXCL10 and IL-6 compared to BT non-reactional controls. None of these individuals had neuritis (29).

HISTOPATHOLOGY

The diagnosis of T1R is usually made clinically but a skin biopsy is sometimes performed to help support the diagnosis. The histological features of a T1R are edema with disorganization of the granuloma and widespread inflammatory cells, largely lymphocytes, and giant cells (see Chapter 2.4). The number of acid-fast bacilli (AFB) may be significantly reduced in borderline lepromatous (BL) leprosy lesions (20). Interestingly, even experienced pathologists may underdiagnose reactions in skin sections from patients with clinically apparent T1Rs (30).

CLINICAL FEATURES

T1Rs predominantly affect patients with the borderline forms of leprosy. A T1R is characterized by acute inflammation in pre-existing leprosy skin lesions, nerves, or both. The development of the severe cutaneous and neurological symptoms of T1R can be a decisive factor in an individual seeking medical advice. Skin lesions become acutely inflamed and edematous and may ulcerate. Edema of the hands, feet, and face can also be a feature of a reaction but systemic symptoms are very unusual. Involvement of the peripheral nerves leads to sensory and motor loss, losses often associated with marked nerve tenderness and nerve pain. A nerve abscess may rarely occur in the context of a T1R, leading to swelling, tenderness, and associated impairment (31) (see Chapter 2.1). A proportion of T1Rs are not associated with demonstrable deterioration in clinical NFI assessed using Semmes Weinstein monofilaments (MF) and voluntary muscle testing (VMT) (see

Chapter 2.5). However, "skin only" reactions are likely to be accompanied by subclinical neuropathy, which often precedes the development of clinically detectable impairment.

T1Rs experienced after the completion of MDT usually occur within three years but may, rarely, occur many years later (32). Late T1Rs can be difficult to distinguish from a leprosy relapse or reinfection (see Chapter 2.4). If the bacterial index (BI) of an individual has increased by two or more units, the individual should be diagnosed with a relapse. However, this measurement requires access to information that may not be available. Furthermore, such an increase in BI will not be observed in PB cases. In dubious cases, a two-week course of oral corticosteroids should improve a T1R whereas symptoms due to relapse will be unaffected (33).

Leprosy T1R reactions occur during pregnancy, particularly in the post-partum period (16). The delivery of a baby is a significant risk factor for having a T1R at the time of leprosy diagnosis (34) (see Chapter 3.2). The restoration of cell-mediated immunity following delivery is thought to trigger the reaction.

ASSESSMENT AND MONITORING

Skin lesions are assessed for erythema, edema, and, rarely, ulceration or secondary bacterial infection. Other cutaneous disorders (see Chapter 2.3) may need to be excluded.

A nerve function assessment is performed using MF and VMT at presentation and monthly thereafter. T1R with facial involvement may be associated with lagophthalmos (35) and a subsequent risk of corneal damage (see Chapter 3.1).

The severity of T1Rs can be measured quantitatively using a validated severity score (see T1R Severity Score) (36). The role of this scale in routine clinical practice has yet to be established.

TREATMENT OF TYPE 1 REACTIONS

The objective of treatment for T1R is to restore clinically normal nerve function and prevent further inflammation-mediated damage. Patients should receive an evidence-based personalized treatment regime where possible, but in some settings a standardized approach may be more appropriate. It is important to explain to affected individuals the nature of the complication. It is also worth reassuring them that they do not pose a risk to family and friends because of the T1R.

The mainstay of treatment for T1Rs is oral corticosteroids. There is no role for topical corticosteroids or other topical immunomodulatory agents, such a topical tacrolimus, in the management of T1Rs. Clinical trials have usually included patients with T1R and/or NFI. NFI lasting longer than six months does not respond to corticosteroid therapy (37); however, it can be difficult to establish the duration of NFI in clinical practice, particularly if the deterioration has been asymptomatic (see Chapter 2.5). Mild adverse effects (AEs) are commonly associated with oral corticosteroid

treatment of T1R. More serious AEs include hypertension, diabetes mellitus, peptic ulceration glaucoma, and tuberculosis (38, 39, 40). Patients prescribed oral corticosteroids should be pre-scribed a gastric acid suppression agent, preferably a proton pump inhibitor. In addition, the need for corticosteroid-induced osteoporosis prevention therapy should be assessed in each individual.

MDT should be started along with the appropriate T1R treatment for those individuals who pres-ent with a T1R when initial leprosy diagnosis is made. MDT should not be stopped for those individuals who develop a T1R while on the therapy. Daily rifampin is a potent inducer of he-patic enzymes that may necessitate increasing the dose of concomitant medications including corticosteroids (41). However, the monthly dose of rifampin in the WHO MDT regime does not necessitate increasing the dose of corticosteroids prescribed to treat T1Rs (or ENL). The recent, large Treatment of Early Neuropathy in Leprosy (TENLEP) trial randomly assigned individuals with NFI (including T1R) of less than six months duration to receive prednisolone for either 20 or 32 weeks (38). Individuals weighing 50 kg or less received a starting dose of 45 mg/day, and those heavier than 50kg received a starting dose of 60 mg. The daily dose of prednisolone was tapered in a standardized fashion in both groups, resulting in no significant difference in clinical outcomes between the groups. The current evidence suggests that individuals should be treated with 0.5–1 mg/kg/day of prednisolone (or equivalent), reduced gradually to zero over the course of 20 weeks. (38, 42) In spite of this evidence, 15% of patients in the TENLEP trial required additional prednisolone to treat exacerbations of T1R as the dose of prednisolone was reduced. Similarly, other studies have found that, despite the use of prolonged courses of corticosteroids and other immunosuppressive agents, between 15–50% of individuals need additional corticosteroids (38, 40, 43).

Administering prophylactic oral prednisolone 20 mg daily for 12 weeks (reduced to zero over a further four weeks) to newly diagnosed MB patients did not reduce the incidence of NFI at 12 months (44). Individuals with NFI that is not responding to medical therapy may benefit from surgical nerve decompression (45), although a Cochrane review did not show any advantage of surgery when compared to medical therapy (46) (see Chapter 4.2). A randomized trial protocol outline of nerve decompression has been proposed to improve the evidence for surgery (47). Physical therapy, reconstructive surgery, and education about self-care may be required in those who have residual permanent NFI (see Chapters 4.1 and 4.2).

Other agents have been compared to prednisolone in the management of T1Rs. Ciclosporin at a starting dose of 7.5 mg/kg/day showed promise in a randomized study of 73 individuals con-ducted in Ethiopia (48). Azathioprine did not have a beneficial effect compared to prednisolone in a randomized controlled trial (43) but may have a role as a steroid-sparing agent (49). There are also case reports of methotrexate being used in T1R (50) and NFI (51) in combination with oral corticosteroids (as a steroid-sparing agent) or alone following their cessation. For individuals with marked neuritis, splinting to support and immobilize the affected area may be used in conjunc-tion with analgesia (52).

Immunosuppressive agents require screening and regular monitoring tests. Local guidelines, where available, should be followed. In settings where none exist, it is prudent for physicians

to identify appropriate guidelines from elsewhere and adhere to them as closely as possible. All patients should be screened for tuberculosis and strongyloidiasis (53) prior to starting immuno-suppressive therapy (see Chapter 3.4). In the case of strongyloidiasis, empirical treatment with ivermectin may be more appropriate and in some settings may need to be repeated at regular intervals (54).

HIV AND TYPE 1 REACTIONS

A Brazilian study of 40 patients with leprosy and HIV co-infection found that 13 (32.5%) developed a T1R. The proportion of individuals with T1R was not significantly different from that of a cohort of HIV-negative leprosy patients reported in the same study (55). However, leprosy T1Rs have been reported as an immune reconstitution inflammatory syndrome (IRIS) in HIV-infected patients treated with anti-retroviral therapy (ART). T1R occurring as an IRIS occurred in almost 50% in the Brazilian study (55). A large study in Rio de Janeiro found ART to be a risk factor for T1R in HIV co-infected individuals (56). The management of T1R in HIV-infected individuals is the same as that in individuals who are not co-infected. (See also Chapter 3.3.)

OTHER CO-INFECTIONS AND TYPE 1 REACTIONS

A cross-sectional study from Nepal found that individuals with evidence of soil transmitted helminth (STH) infestation were less likely to have a "leprosy reaction" than those without. (57) Sixty percent (60%) of those who had a "leprosy reaction" had a T1R. The potential protective association of STH with leprosy warrants further investigation.

The results of a study of leprosy and viral co-infection with human T-cell lymphotrophic virus type 1, hepatitis B, and hepatitis C suggest that they might be associated with increased rates of NFI. However, the study was too small to draw meaningful conclusions (58). However, patients should be screened for these infections where appropriate. (See Chapter 3.4.)

Erythema Nodosum Leprosum

The term ENL was first suggested in 1912 by Murata, who recognized that the condition "may be acute, subacute, or chronic" (59). ENL reactions are also sometimes called Type 2 reactions.

EPIDEMIOLOGY

ENL affects individuals with BL leprosy and lepromatous leprosy (LL). It may also occur in a small percentage of individuals with borderline (BB) leprosy (60). Approximately 10% of people with

BL leprosy and up to 50% of those with LL will develop ENL (60, 61). A systematic review of the epidemiological data on ENL reveals incidence rates ranging from 1 to 8 per 100 person years at risk (60) (Table 1).

The mean bacterial index (BI) at diagnosis indicates an individual's risk for developing ENL. Specifically, the odds of an individual with BL leprosy and a BI≥4 at diagnosis developing ENL is 5.2 times greater than that of an individual with BL leprosy and a BI<4 (61).

ENL occurs during pregnancy and the post-partum period (62) (see also Chapter 3.2). However it is unclear whether pregnancy increases the risk of ENL (16). No prospective studies of the association of pregnancy and ENL have been conducted in the MDT era.

TABLE 1 Incidence rates of ENL

Study	Study location/type	Population at risk	Method of classification	Number of cases of ENL	Number at risk	Cases (Episodes*)/100 PYAR
Bangladesh (13)	Field	MB	Clinical and SSS	8	357	1.1
Ethiopia (63)	Field	MB	Clinical and SSS	16	300	6.9*
Bangladesh2 (64)	Field (Retrospective)	MB	Clinical	10	471	1
Thailand (9)	Hospital	BL/LL	Skin biopsy	44	119	3.9
Nepal (65)	Hospital (Retrospective)	BL/LL	Skin biopsy	22	175	3.2*
India (66)	Hospital	BL/LL	Skin biopsy	21	105	7.6

PATHOGENESIS

The pathogenesis of ENL is unclear. It was argued that ENL is an immune complex-mediated disease because of its similarity to the Arthus reaction and because of evidence of deposition of complement proteins and immunoglobulins in the dermis of skin biopsies from patients (67). However, these studies do not demonstrate the deposition of immune complexes in affected tissues (68). A deficiency of complement protein C4B has been associated with an increased risk of ENL and with immune complex-mediated diseases (69).

ENL has been associated with lower levels of regulatory T-cells and higher CD4/CD8 ratios than those found in LL control groups without ENL (70). The increased CD4/CD8 ratio has been found in both the skin and blood of patients, providing support for the involvement of T-cells in ENL (68).

TNF-α appears to be an important inflammatory mediator in ENL but its role in ENL initiation is unclear. Studies have shown highly variable levels of plasma and serum TNF-α in patients with ENL. The inconsistencies in these data are likely due to study design and, possibly, differences between the populations studied (68).

IFN-γ has been associated with an increased frequency of ENL when injected intradermally in patients with LL. Studies have also shown that IFN-γ is increased in the serum and skin of patients with ENL (68).

Recent gene expression studies have suggested that neutrophil recruitment (71) and complement activation (72) play a role in ENL.

HISTOPATHOLOGY

In ENL, skin lesions show a perivascular infiltrate of neutrophils in the dermis and subcutis, but neutrophils are not always present (see Chapter 2.4). A necrotizing vasculitis and features of a lobular panniculitis may be present. The number of neutrophils in a skin biopsy diminishes with the age of the lesion.

CLINICAL FEATURES

ENL is characterized by crops of tender, erythematous skin lesions, often accompanied by fever and malaise. ENL affects numerous organ systems and is an extremely painful condition. In a cross-sectional study, 20% of the patients had a fever, with more than 75% with a history of fever prior to being examined (73). Peripheral edema of the limbs and face is common in patients with ENL (73).

Skin

The typical ENL skin lesion is an erythematous, tender papule or nodule (73). Subcutaneous nodules also occur. Skin lesions may be vesicular, pustular, or bullous. Lesions may ulcerate and become necrotic. Erythema multiforme-like skin lesions have also been reported (73, 74). A desquamative eruption may occur, which is rare, and needs to be distinguished from a drug eruption. Lesions may heal with scarring that may become inflamed when the ENL flares-up. In rare cases, there may be no skin lesions suggestive of ENL (75).

Nerve function impairment (NFI)

NFI was present in over 50% of the cohort in a multicenter ENLIST 1 cross-sectional referral clinic-based study. Nerve involvement in ENL may be severe but is usually less marked than in T1R.

Arthritis and dactylitis

Both large and small joints are frequently affected in ENL. Arthralgia is very common, but true arthritis also occurs in more than 20% of patients with ENL (73). Distal and proximal polyarthritis has been described. Patients may experience joint inflammation that resembles rheumatoid arthritis with a symmetrical polyarthritis (76). A false-positive rheumatoid factor occurs in patients with LL (77). Erosions on plain radiographs have also been documented. Swelling and inflammation of a digit (dactylitis) occurs less frequently.

Lymphadenitis

ENL-associated lymphadenopathy is usually painful and occurs in approximately 15% of cases. It may cause diagnostic confusion with lymphoma. Lymph nodes may suppurate (78).

Orchitis

Although under recognized, testicular tenderness, and more severe inflammation, has been reported to occur in 13.5% of men with ENL (73). Swelling and severe pain may occur. Recurrent orchitis due to ENL has been implicated as a cause of testicular dysfunction in leprosy patients (79).

Rhinitis and the respiratory tract

Nasal involvement in ENL occurs in approximately 8% of patients and may lead to septal perforation (73, 80). The nose becomes painful and obstructed by edema. Laryngeal involvement in ENL, although very uncommon today, is potentially life threatening (81). The symptoms include pain, stridor, hoarse voice, and aphonia. One patient described by Fleury et al. required a permanent tracheostomy due to secondary scarring (81). In addition, there are occasional reports of pulmonary infiltrates associated with ENL, which may cause confusion with tuberculosis (82).

Ocular involvement

ENL is associated with iridocyclitis (also known as anterior uveitis or iritis), episcleritis, and scleritis (see Chapter 3.1) (83). Ocular inflammation was reported in 5% of the ENLIST 1 study cohort (73). In addition, ENL has been reported to result in perforation of the globe, requiring enucleation (84).

Other organ systems

Hepatosplenomegaly is very rare; however, hemophagocytic syndrome has been associated with ENL (85). Secondary amyloidosis causing renal impairment was a significant problem in patients with LL, particularly those who had ENL prior to the introduction of MDT (86, 87). ENL may be as-

sociated with nephrotic syndrome and acute glomerulonephritis, but its connection to glomeru-lonephritis is not clear (88).

ASSESSMENT AND MONITORING

Symptoms of fever and skin or other organ involvement result in a wide differential diagnosis, which may delay a diagnosis of ENL (and leprosy in those who present with ENL). It is important in leprosy endemic countries (or in individuals from those countries) to consider ENL as a cause of these symptoms in addition to diseases such as Sweet's syndrome, vasculitis, and connective tissue disorders (see Chapter 2.3). Physicians should bear in mind that false-positive serological tests may lead to diagnostic confusion in LL patients (77, 89).

Patients should be carefully assessed with respect to their pain and cutaneous, joint, and eye involvement. In particular, it is important to ask patients about nasal and testicular symptoms, as the involvement of these organs is often overlooked.

Peripheral nerve function should be carefully assessed and monitored at each visit using mono-filaments (MF) and voluntary muscle testing (VMT). A scale has been developed and validated for measuring the severity of ENL, although its role in routine clinical practice has not been defined (90). The scale is available at ENL Severity Scale.

TREATMENT

The management of ENL can be challenging due to the often chronic nature of the condition and the adverse effects of treatment. Hospital-based studies show that the majority of patients with ENL have chronic disease, which can continue to cause problems for many years (61, 73, 91, 92). Individualized treatment is essential in these patients, who often experience flare-ups in the illness when treatment is reduced. It is also important that patients with ENL and their relatives be given information about ENL and its management.

In Ethiopia, ENL patients were shown to have an increased mortality rate compared to patients with T1R (93), with corticosteroids implicated in the majority of deaths. ENL was associated with considerable mortality in the pre-MDT era, largely due to renal failure (94). Untreated ENL carries a well-recognized risk of death and suicide. Those individuals already taking WHO MB MDT should continue that treatment as well as commence specific treatment for ENL. Those presenting with ENL should begin MDT as well as the treatment for ENL.

There is a lack of robust data to inform treatment decisions for ENL, particularly regarding steroid-sparing agents. In the MDT era, less than 300 patients have participated in randomized ENL treatment trials of variable quality. Furthermore, the availability, cost, and acceptability of the drugs used to treat ENL all play a role in whether patients get the most effective and safest regime to control their disease. While MDT is provided free of charge to leprosy patients, the drugs used to

treat reactions are not universally free. ENL has been shown to be associated with a significant economic burden that predisposes affected individuals and their families to greater levels of economic hardship (95).

A Cochrane review of interventions for ENL published in 2009 found that, although the eligible studies were of low quality, they provided evidence of the benefits of thalidomide and clofazimine (96). Since the review was published further data from randomized trials of prednisolone (97, 98, 99), thalidomide (97, 99), clofazimine (99, 100), pentoxifylline (100), and ciclosporin (98) have been published, as have case series of patients treated with minocycline (101), methotrexate (102), and azathioprine (103).

Prednisolone

Oral and parenteral corticosteroids rapidly control the symptoms of ENL. Doses of 1–2 mg per kg body weight are usually required. There are no data from controlled studies regarding the treatment of the neuritis or iridocyclitis associated with ENL. The minimum dose required to control symptoms should be employed, but as the dose of corticosteroid is reduced, the ENL often flares. Tachyphylaxis occurs with flares of ENL at even higher doses of steroids. The prolonged exposure to high doses of corticosteroids leads to adverse effects (91, 104) and is associated with mortality (93). Fatal cases of *Strongyloides stercoralis* hyperinfection following steroid treatment of ENL have been reported (105) (see Chapter 3.4).

Thalidomide

Thalidomide, whose use in ENL was first reported by Sheskin in 1965 (106), is very effective in the management of ENL. A starting dose of 300–400 mg per day is used (91, 92, 107). The dose is adjusted according to symptoms or if adverse effects occur. In a study by Nabarro et al., the median duration of thalidomide therapy was 16 months (108). The "neuritis" associated with ENL (measured using motor conduction velocities) was reported to improve with thalidomide (109), but the study needs to be repeated. According to Sheskin, thalidomide was effective in the control of iritis associated with ENL both when used alone (or in conjunction with mydriatics) (110) and when used in combination with a steroid containing eye drops (111).

The mechanism of action of thalidomide in ENL remains unclear but has been attributed to an anti-TNF-α effect. However, as Naafs and Noto have questioned: why then is it ineffective for T1Rs (112)? Recently it has been shown that thalidomide and its analogues cause teratogenicity and exert their therapeutic effect in myeloma by binding to the ubiquitination protein cereblon (113). Lenalidomide prevents Rabex 5 from binding to cereblon and reduces toll-like receptor-mediated inflammatory activation (114). However, there are data in mice suggesting that thalidomide may exert its anti-inflammatory effect on toll-like receptors independently of cereblon (115).

Thalidomide causes a wide range of congenital abnormalities and almost any organ system may be affected (116). 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 system after the limbs. The teratogenic effect of thalidomide occurs when it is taken from 20 to 36 days after conception. The drug is present in human semen after ingestion (117), but there are no reports of teratogenicity caused through exposure to the semen of men on thalidomide.

Physicians must undertake a detailed assessment of the risks as well as the benefits before pre-scribing thalidomide. For female patients, pregnancy should be excluded prior to starting tha-lidomide and the use of adequate contraception strongly recommended. The patient and his/her partner should be educated about the drug and the associated adverse effects. Only one month's supply of thalidomide should be prescribed to ensure that regular monthly assessments and pregnancy tests are negative before additional doses of the drug are dispensed. Patients should be specifically told not to share the medication under any circumstances. Finally, usage should conform to local guidelines and prescribing programs.

Thalidomide neuropathy manifests as painful paranesthesia and/or numbness. The feet are af-fected before the hands in a glove-stocking type distribution. Weakness may also occur. Nerve conduction studies show a predominantly sensory, axonal, length-dependent neuropathy. Nerves show loss of large myelinated fibers and little inflammation when examined histologically (118). 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 (119). The neuropathy correlated with the daily dose administered and became permanent for 50% of those individuals. The neuropathy may progress for some time after ces-sation of the drug (118), and any improvement that does occur may do so slowly. There are no data concerning neuropathy attributable to thalidomide in individuals with ENL. Sheskin and Yaar did not observe any thalidomide neurotoxicity in 26 ENL patients monitored with motor nerve conduction studies (120), nor did Magora et al. in 13 patients assessed using both sensory and motor nerve conduction (121). The role of regular nerve conduction studies in patients with ENL who are receiving thalidomide is not well defined, and such investigations are often not readily available. Physicians should enquire about neurological symptoms at each assessment.

Thromboembolism has been reported in numerous patients with ENL who have been treated with a combination of thalidomide and corticosteroids, but the exact risk is unclear (122, 123). Thalidomide increases the risk of arterial and venous thromboembolism, a risk that appears to increase with the concomitant use of corticosteroids (124). Patients with myeloma receiving tha-lidomide, lenalidomide, or pomalidomide routinely receive prophylaxis for thromboembolism. Darlong and colleagues reported using aspirin when treating ENL patients with thalidomide to prevent thromboembolism (91).

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 (125). Other adverse effects that may lead to discontinuation of thalidomide include bradycardia, dizziness, nausea,

peripheral edema, dyspnea dermatitis, neutropenia, erectile dysfunction, and amenorrhea. Hypothyroidism has also been reported following the administration of thalidomide (126).

Clofazimine

Treatment with clofazimine, a mild anti-inflammatory agent, improves ENL (127). However, clofazimine therapy does not control severe ENL and takes four to six weeks to become active (128). Clofazimine monotherapy for ENL is suggested in individuals in whom corticosteroids are contraindicated (128), but in practice it appears that it is used as a steroid-sparing agent (73).

The WHO recommends that clofazimine be administered at 300 mg per day for 12 weeks, then reduced to 200 mg for 12 weeks and maintained thereafter at 100 mg for 12–24 weeks (128). At this dose, the drug often worsens clofazimine pigmentation, which may be unacceptable to patients. Furthermore, there is an increased risk of clofazimine crystal enteropathy (129, 130), and possibly cardiotoxicity (131), at the larger doses used to manage ENL.

The daily dose of 50mg in MB MDT probably protects at-risk individuals from ENL. This assumption has never been formally tested, but a multicenter study of different chemotherapy regimes in patients with LL showed that regimes containing clofazimine given 100mg three times a week for five years were associated with a lower rate of ENL (132). Any protective effect of clofazimine is lost after one year, when MB MDT is stopped. In patients treated with 12 months of MB MDT, there was no increase in the frequency of ENL, but it was more severe in that group compared to a separate cohort treated with 24 months.

Pentoxifylline

Pentoxifylline, a methylxanthine derivative, has been shown to inhibit the production of TNF both *in vitro* and *in vivo* (133). A randomized double-blind study in which 1.2g of pentoxifylline was administered daily for ENL demonstrated that it was not as effective as 300mg thalidomide administered daily (107). In addition, it was associated with significant rates of adverse effects.

Ciclosporin

Ciclosporin, at an initial dose of 7.5 mg per kg per day compared to prednisolone, showed promising results in a small double-blind randomized controlled trial of 7 patients with newly diagnosed ENL. However, it did not appear to have an impact on 10 chronic ENL patients (98).

Methotrexate

Methotrexate is widely available and affordable in many leprosy-endemic countries. There are three reports of oral methotrexate being used to treat chronic ENL at initial <u>weekly</u> doses of 7.5 mg (102) and 15 mg (134, 135).

Azathioprine

The use of azathioprine for ENL has been described in case reports and a case series. In the Brazilian case series of nine patients, azathioprine was used at initial doses of 2–3 mg per kg body weight daily (103). Eight patients benefitted from the azathioprine, but it was discontinued in one patient due to drug-induced hepatitis. There was no assessment of thiopurine methyltransferase activity in these nine patients.

Minocycline

A pilot study of 100 mg of minocycline administered daily to 10 patients with prednisolone-dependent chronic ENL has shown promising results (101). However, minocycline-induced pigmentation occurred in all of the patients.

TNF-α biological drugs

The chimeric anti-TNF-α monoclonal antibody infliximab (136) and the recombinant TNF-α receptor fusion protein etanercept (137, 138, 139) have been used to treat ENL in four individuals.

Other drugs

The following drugs have also been used to treat ENL. Chloroquine therapy is occasionally used to manage ENL, but there is little evidence from controlled studies that it is effective (140). The leukotriene antagonist zafirlukast at a dose of 40mg twice daily was effective in six patients with ENL, although outcome measures were not defined (141). Colchicine has been used to treat ENL but appears to have a limited effect (142). Oral zinc has been used in two small uncontrolled studies (143, 144). Finally, levamisole given on three consecutive days monthly for three months was found to be ineffective (145). In the ENLIST 1 study, no patients had been treated with any of these at the time of enrolment in the study (73).

HIV AND ENL

There are case reports of ENL presenting as an IRIS following the initiation of ART (146, 147), but no suggestion that this process is different than that in patients who are not HIV infected. HIV

causes a neuropathy and thalidomide is contraindicated in patients with HIV neuropathy (148). Thalidomide has been used in HIV-infected individuals to treat papular pruritic eruption (149), nodular prurigo (150), and aphthous ulceration (151), but in lower doses than in ENL. In some of these latter patients, neurotoxicity limited the use of thalidomide (150) and a rash occurred in a high proportion (151). (See also Chapter 3.3.)

OTHER CO-INFECTIONS AND ENL

The odds of a leprosy patient with ENL having any type of co-infection are more than twice as high as those of a patient with no evidence of a reaction (152). The Brazilian study (57) was cross-sectional, so it is not possible to determine whether the co-infections may trigger ENL. It is plausible that patients with ENL are more susceptible to such infections due to immunosuppression. The authors of the Brazilian study describe co-infections in both T1Rs and ENL (57); however, they did not report the infections for each type of reaction separately. The co-infections included oral and sinus infections, urinary tract infections, viral hepatitis, intestinal parasites, pneumonia, syphilis, tuberculosis, leishmaniasis, and staphylococcal infections (152). In cases of ENL that are refractory to treatment, it may be worth considering the presence of concomitant infections. (See Chapter 3.4.)

Lucio's Phenomenon

Lucio's phenomenon is a complication of diffuse non-nodular LL (Lucio's leprosy, see Chapter 2.1) (153). Lucio's phenomenon is rare and was originally thought to be confined to Mexico, where Lucio's leprosy was first described. However, cases have been reported from various geographic regions (154). Lucio's phenomenon occurs in infections with either *M. leprae* or *M. lepromatosis* (see Chapter 2.4).

Lucio's phenomenon is characterized by erythematous, irregular macules that become purpuric and then necrotic, usually developing on the distal lower limbs. The upper limbs, trunk, and face are subsequently involved. A secondary bacterial infection of the skin and septic shock may result from extensive cutaneous involvement. Healing leaves atrophic scars, but extensive tissue necrosis may require amputation.

The histopathology of skin lesions from patients with Lucio's phenomenon shows endothelial proliferation, bacilli within the endothelium, luminal occlusion, and thrombosis, which result in cutaneous necrosis (154) (see Chapter 2.4). The severe nature of the skin necrosis constitutes a medical emergency. Treatment with MDT alone results in clinical improvement and healing of tissue (154, 155), but in patients with severe, exfoliating lesions, additional supportive treatment may be necessary. In some cases, surgical debridement of non-viable tissue is necessary.

In practice it may be difficult to distinguish clinically between Lucio's phenomenon and the necrotic lesions of ENL or other causes of severe cutaneous necrosis such as vasculitides. This difficulty results in patients often receiving MDT and/or corticosteroids. Once the diagnosis has been established, any immunosuppression that has been commenced should be stopped in an appropriate manner. The picture is further complicated by the fact that ENL may occur in patients with diffuse non-nodular LL (154). The distribution of cutaneous necrosis, particularly in the early stages, supports the hypothesis that the pathophysiology is due to vascular occlusion rather than the systemic immune activation of ENL. Further research with clearly defined clinical and histological criteria will help to clarify the cause and optimal treatment of Lucio's phenomenon.

Leprosy reactions are a cause of severe morbidity and have a profound negative impact on affected individuals. The NFI associated with reactions that leads to disability needs to be diagnosed and treated promptly. Patients diagnosed with leprosy should be warned about the possibility of reactions, how to recognize them, and whom to contact if they suspect a reaction has developed. It is important to constantly reassure individuals affected by reactions that they are neither an adverse effect of MDT nor a sign of active infection, and that they will ultimately resolve.

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