Drugs of the Future 2006, 31(11): 961-967
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CCC: 0377-8282/2006
DOI: 10.1358/dof.2006.031.11.1036836

Review Article

Leprosy: epidemiology and present and possible future therapeutic approaches

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CONTENTS

Abstract

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* and is associated with hypersensitivity reactions. Because of the consequences of the potential complicating neuritic and ocular involvement, it remains one of the leading causes of permanent physical disabilities. Approximately 83% of leprosy cases are found in the relatively highly endemic countries of Nepal, Madagascar, Myanmar, Indonesia, and especially India and Brazil. The current multiple drug therapy regimens have significantly reduced its prevalence, but unfortunately its incidence has remained about the same over the last 10 years and raises concern about the concept that the current effective therapy not only can reduce the transmission but also the incidence. Among the therapeutic and control measures being sought to help eliminate leprosy are: 1) tools for detecting preclinical disease; 2) a shorter duration of therapy by utilizing other more bactericidal drugs; 3) improvement in the ability to predict and treat more effectively reactional episodes; 4) new methods for better detection and treatment of neuritis and ocular involvement; 5) a clearer understanding of the mode and pattern of transmission; 6) the establishment of risk factors for infection; 7) the development of a practical and effective vaccine; and 8) the removal of the stigma of leprosy through widespread education.

Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae,* which preferentially affects the skin, superficial peripheral sensory, autonomic and motor nerves, the anterior chamber of the eye and the upper respiratory tract. Leprosy patients have to contend not only with the bacterial infection but also with the potential complications of immunological hypersensitivity reactions to *M. leprae* antigens (1-4).

Epidemiology

M. leprae, an obligate intracellular organism found predominantly in macrophages, nerves and smooth muscle of the skin, was identified by Hansen in 1873. The organism divides by binary fission, is Gram-positive and strongly acid-fast, and it cannot be cultured. It has a generation time of 13 days and its optimal growth temperature is 27-30 °C, which explains its predilection for the cooler parts of the body, the skin, upper respiratory tract, superficial nerves, anterior chamber of the eye and testes. *M. leprae* can survive 45 days outside the body and it has been found in soil, armadillos and mangabey, rhesus and African green monkeys (5, 6).

The factors predisposing an individual to infection are impaired cell-mediated immunity to *M. leprae*, prolonged exposure to a sufficient number of organisms, genetic predisposition and socioeconomic environmental factors, such as close living quarters and lack of adequate nutrition. Unlike tuberculosis, HIV disease has not demonstrated a significant impact on leprosy, and *vice versa*; however, there may be a minor increase in the incidence of reversal reactions resulting from an immune reconstitution phenomenon (7, 8).

It has been suggested that 95% of adults are not susceptible to the disease. The incubation period is 2-7 years, but can be as long as 30 years. The incidence of conjugal leprosy is 2-7%. Areas being actively pursued in the search for a genetic predisposition to leprosy are the HLA system, class TT alleles, NRAMP (natural resistance-associated macrophage protein), vitamin D receptor, tumor necrosis factor-α (TNF-α), the promotor polymorphic chromosome/op 13 gene, the toll-like receptor (TLR) family and the leukocyte immunoglobulin-like receptor (LTR) family (9).

In 1981, the number of leprosy patients worldwide was more than 12 million. With the implementation of multiple-drug therapy (MDT) in 1982, more than 10 million patients were “cured” over the following 10 years. The

global prevalence of 12 per 10,000 in 1985 fell to slightly below 1 per 10,000 in 2002. In 2000, 719,330 new cases were diagnosed. In 2002, of the 122 countries where leprosy was considered endemic, 107 had achieved the "elimination target" (1 per 10,000) and the number of new cases has remained the same during the last 10 years. Approximately 83% of leprosy cases are found in 6 countries: Nepal, Madagascar, Myanmar, Indonesia, and especially India and Brazil. As of 2001, there were 6,518 "active" cases registered in the U.S. (10, 11).

In the 1960s, two great advances in the field of leprosy were made and led not only to a dramatic increase in our understanding of the disease but also its treatment. These advances comprised the Ridley-Jopling classification based on the host's immunity to *M. leprae* and the discovery by Shepherd that the bacilli could be grown in the footpad of mice, a model which can be used to determine the resistance of *M. leprae* to therapeutic drugs (6).

The seventh meeting of the WHO Expert Committee on Leprosy in 1998 defined a case of leprosy as an individual who has not completed a course of treatment and has one or more of the cardinal signs: 1) a hyperpigmented or reddish skin lesion with loss of sensation; 2) involvement of the peripheral nerves, as demonstrated by thickening and associated loss of sensation; 3) skin smear positive for acid-fast bacilli (12).

Leprosy can rarely present as a purely neural disease without skin lesions, so-called neuritic leprosy, which can be confirmed by nerve biopsy.

In 1966, Ridley and Jopling created a classification of leprosy based on the degree of the host's capacity to mount a cell-mediated immunological response to *M. leprae*. The host's cell immunity to *M. leprae* dictates the clinical manifestation, the bacteriological load of lesions, the histopathological picture and the prognosis, the type of therapy and the response to therapy (13).

In 1998, the WHO Expert Committee on Leprosy declared that skin slit smears were not essential to classify the disease to determine the intensity of treatment. They recommended that the number of clinical lesions present be the basis for classification. Patients who are not experiencing a reaction and have 5 lesions or less are classified as paucibacillary (PB), and those with 6 or more lesions are classified as having multibacillary (MB) disease (12, 14). However, some MB cases may be classified as PB, which could result in inadequate therapy. Fortunately, skin smears and/or biopsies are available to patients in the U.S., and if organisms are detected they are treated as having MB disease.

Acute inflammatory episodes may occur during the course of chronic infection with *M. leprae* and may appear before, during or after therapy. These episodes occur in as many as 25-30% or more of borderline or lepromatous patients and may occur with neuritis or as a silent neuropathy, which is characterized by a progressive sensory or motor loss without obvious clinical signs of neuritis. This is considered to be a hypersensitivity reaction to *M. leprae* antigens. There are three types of reaction: the reversal reaction (so-called type 1 reaction), erythema nodosum leprosum (ENL, or type 2 reaction) and Lucio's phenomenon (15, 16).

Treatment

The principles of therapy are based on early detection of disease, appropriate and adequate therapy to prevent disabilities, and rehabilitation to minimize the physical, psychological and socioeconomic impact of the resulting disabilities. Therapy must be tailored to the type of nonreactive disease, the nature of the complicating reactive disease (type 1, type 2 or Lucio's phenomenon), the presence of neuritis and its complications (ulcerations of skin due to insensitivity or paralysis caused by motor nerve involvement), and ocular disorders (exposure keratitis, iritis, scleritis and glaucoma). Modification of the current recommended programs for PB and MB disease may be necessary due to the current long duration of therapeutic regimens, drug reactions or intolerance, and possibly drug resistance (9, 17, 18).

In 1981, the WHO Study Group recommended MDT for the following reasons: 1) to address dapsone resistance and to prevent the development of resistance to other drugs used; 2) to move away from long-term monotherapy with dapsone; 3) to include rifampin in all therapeutic regimens because of its potent bactericidal action and its efficacy given as infrequently as once a month; 4) to promote compliance through shorter duration and greater supervision of therapy and cost-effectiveness (19).

Currently the three standard antileprosy drugs recommended in the therapy of PB and MB disease are dapsone, rifampin and clofazimine (Table I). The WHO-recommended treatment for PB and MB disease and the treatment recommended by the National Hansen's Disease Program in the U.S. are depicted in Table II. Other drugs with antimycobacterial properties which may be used as substitutes in the current regimens or in new field trials are rifabutin, ofloxacin, sparfloxacin, levofloxacin, minocycline and clarithromycin.

Antibiotic resistance is assessed by the failure of clinical responses and can be substantiated by mouse footpad studies or by using the sequence of *M. leprae* genome-specific oligonucleotides and PCR to recognize mutations for resistance to rifampin, ofloxacin and dapsone (18-20).

In general, the recommended therapeutic regimens for PB and MB disease are satisfactory, but limitations include the occasional occurrence of persistent disease activity with later reversal reactions and relapse in PB disease, and the persistence of live and dead organisms in MB disease with late recurrent ENL reactions and accompanying neuritis and relapses. However, the drive to develop new drugs or novel therapeutic approaches may be compromised by the relative efficacy of current therapeutic regimens and the fact that these drugs are provided free through the global alliance program for the elimination of leprosy.

Table I: Current antileprosy drugs.*

Drug	Dose	Adverse events	Antibacterial mechanism	Drug interactions
Dapsone	100 mg/day	Anemia, hemolysis (G6PD), methemoglobinemia, agranulocytosis, liver toxicity, sulfone syndrome, peripheral neuropathy	Weakly bactericidal; competitive PABA antagonist	Substrate for CYP2C9, 2E1 and 3A4; increases marrow toxicity of zidovudine (Retrovir) and pyrimethamine (Duraprim); increases serum trimethoprim levels
Clofazimine (Lamprene)	50 mg/day	Nausea, skin pigmentation and xerosis, bowel motility/ileus, possible cardiac arrhythmias	Weakly bactericidal; binds mycobacterial DNA	None confirmed
Rifampin (Rifadin)**	600 mg/day (given as monthly dose if concurrent steroids used)	Nausea, hepatotoxicity, marrow suppression, interstitial nephritis, flu-like syndrome, discolored body fluids, drug interactions	Bactericidal; inhibits DNA-dependent RNA polymerase	Strong inducer of CYP3A4; decreases levels of corticosteroids, estrogens, protease inhibitors, carbamazepine (Tegretol), macrolides, methadone (Dolophine), and others
Minocycline (Minocin)**	100 mg/day	Nausea, deposits in bone and teeth, photosensitivity, hyperpigmentation, CNS toxicity, hypersensitivity	Bactericidal; inhibits ribosomal protein synthesis	Decreased absorption with cation preparations; decreases effect of estrogens; increases effect of warfarin (Coumadin)
Ofloxacin (Floxin)**	400 mg/day	Nausea, CNS toxicity, phototoxicity, hypersensitivity, drug interactions	Bactericidal; inhibits DNA gyrase	Increases effect of theophylline (Uniphyl), caffeine, warfarin (Coumadin), antiarrhythmics; absorption decreased by didanosine (Videx) and cationic preparations
Levofloxacin (Levaquin)**	500 mg/day	Nausea, CNS toxicity, phototoxicity, hypersensitivity, drug interactions	Bactericidal; inhibits DNA gyrase	Increases effect of theophylline (Uniphyl), caffeine, warfarin (Coumadin), antiarrhythmics; absorption decreased by didanosine (Videx) and cationic preparations
Clarithromycin (Biaxin)**	50 mg b.i.d.	Nausea, motility disorders, cardiac arrhythmias, hypersensitivity, drug interactions	Bactericidal; inhibits ribosomal protein synthesis	CYP3A4 substrate, also inhibits CYP1A2 and 3A3/4; increases levels of theophylline (Uniphyl), ciclosporin (Neoral), carbamazepine (Tegretol), cisapride (Propulsid), astemizole (Hismanal)*** and others

*Joyce, M.P., Scollard, D.M. *Leprosy (Hansen's disease)*. In: Conn's Current Therapy. Rakel, R.E., Bope, E.T. (Eds.). Elsevier, 2004, 102. **Not FDA-approved for this indication. ***Not available in the United States. CNS, central nervous system; CYP, cytochrome P-450; G6PD, glucose-6-phosphate dehydrogenase deficiency; PABA, *para*-aminobenzoic acid; TB, tuberculosis

In an attempt to shorten and simplify therapy, trials are ongoing evaluating a combination of rifampin, ofloxacin and minocycline (ROM) (21). Trials include single-dose ROM (rifampin 600 mg, ofloxacin 400 mg and minocycline 100 mg) for a single lesion; ROM monthly for 6 months in PB disease and for 12 months in MB disease; rifapentine, moxifloxacin and minocycline (P*M*M) as a single dose for PB and MB disease; and rifampin and ofloxacin (RO) daily for 1 month in all types of leprosy (22). At least 5-10 years will be needed to assess the efficacy of these trials.

Animal models have demonstrated that rifapentine and the newer fluoroquinolones (levofloxacin, moxifloxacin and sitafloxacin) are more bactericidal than rifampin and ofloxacin (23).

Table II: Treatment regimens for leprosy.

	World Health Organization (WHO)	U.S. National Hansen's Disease Program
Paucibacillary (PB) disease		
Dapsone	100 mg/day for 16 months	100 mg/day for 12 months
Rifampin	600 mg monthly under supervision for 6 months	600 mg/day for 12 months
Multibacillary (MB) disease		
Dapsone	100 mg/day for 12 months	100 mg/day for 24 months
Rifampin	600 mg monthly under supervision for 12 months	60 mg/day for 24 months
Clofazimine	50 mg/day plus 300 mg each month under supervision for 12 months	50 mg/day for 24 months (alternative drug minocycline 100 mg/day for 24 months)

Newer drugs being tested in mouse footpad studies and limited clinical trials as monotherapy or in combination include rifapentine, moxifloxacin and HMR-3647 (21, 23).

Rifapentine, a rifamycin derivative with higher peak serum concentrations and a much longer serum half-life, has been found to be more effective than a single dose of rifampin alone or in combination with ROM in killing *M. leprae* in mouse footpads.

Moxifloxacin is a new broad-spectrum fluoroquinolone that has been found to be the most active fluoroquinolone against *Mycobacterium tuberculosis* in mice and against *M. leprae* in mouse footpads. Its bactericidal activity is identical to that of a single dose of rifampin.

HMR-3647 (telithromycin) represents a new class of macrolides, the so-called ketolides. It has significant bactericidal activity against *M. leprae* equal to or slightly greater than clarithromycin, which has been used in the past in combinations as a substitute for one of the current standard drugs.

A single-dose combination of rifapentine, moxifloxacin and minocycline, which killed 99.9% of viable *M. leprae* in mouse footpads, appears to be more bactericidal than a single dose of ROM or rifampin alone. In the same study, moxifloxacin plus minocycline was more bactericidal than the combination of ofloxacin/minocycline (23).

Treatment of reactions and neuritis

Treatment of type 1 reaction (reversal reaction) (24-26) depends on the severity of skin involvement (edema, ulceration), the severity of associated neuritis, facial involvement (edema and the potential underlying facial nerve involvement), pregnancy and a history of adverse or allergic drug reactions. The reversal reaction with no neural involvement usually subsides spontaneously during continued therapy for nonreactive disease. However, facial involvement with significant inflammatory edema with or without ulceration requires prednisone, initially at a dose of 40-60 mg daily and tapered according to the response to therapy. Those with associated neuritis require higher doses of prednisone given for at least 3-6 months. Ciclosporin has been reported to be effective, although relapse occurs upon discontinuation (27). Therapy of PB should be continued. The use of clofazimine in type 1 reaction is controversial, although it may be worth trying in cases less responsive to systemic corticosteroids.

Type 2 reactions (28) can be mild or severe, of short or long duration (usually 1-2 weeks), or recurrent over extended periods. Mild cases have cleared spontaneously or have responded to mild antiinflammatory drugs such as aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), antimalarials, colchicine (29) and pentoxifylline (30). Moderate to severe reactions, especially with associated neuritis, are treated with prednisone at doses sufficient to treat the constitutional signs of fever and malaise, arthritis, neuritis, skin lesions and orchitis. Ocular lesions are treated with topical steroids and atropine until seen by an ophthalmologist. If the response is slow or the doses of prednisone are compromised by side effects or associated medical conditions such as diabetes, hypertension, glaucoma, osteoporosis or uncontrollable gastric ulcer disease, clofazimine at doses up to 300 mg/day may be used. If control is not achieved by the above approach, thalidomide 100-300 mg/day may be used initially and tapered according to the patient's response (31). The drug should not be given to pregnant women and women of childbearing age should use at least two birth control methods. The potential neurotoxicity of thalidomide therapy and its impact on neuritis of lepromatous leprosy have not been adequately addressed in leprosy. The possible role of the immunosuppressive drugs azathioprine, mycophenolate mofetil and ciclosporin needs to be investigated for potential prednisone-sparing or replacement in type 1 and type 2 reactions. Anti-TNF biologics, such as etanercept, adalimumab and infliximab (32), have reportedly been effective in ENL, although they are very costly and usually adversely affect infection, especially mycobacterial infection. Consequently, they should be used in very unusual circumstances with adequate MB therapy coverage.

The most significant side effects of thalidomide (33, 34) are teratogenic (seal limbs) and polyneuropathy, which is a symmetrical sensory motor type. The severity of these reactions is related to dose and the duration of therapy. Among other side effects are the following: 1) nervous – drowsiness, convulsions, paresthesias; 2) cutaneous – dryness, xerosis, facial and distal edema,

erythema, urticaria; 3) gastrointestinal – nausea, constipation, increased appetite; 4) hematological – leukopenia; 5) miscellaneous – fever, increased weight, amenorrhea; 6) presence in human semen.

Analogues of thalidomide have been developed that can be grouped into two distinct families (35). One group inhibits the production of TNF-α and phosphodiesterase type 4 (PDE4) but does not inhibit monocytic IL-6 and stimulates the production of IL-8 and IL-10. The second group inhibits the production of TNF-α, IL-6 and IL-8, but does not inhibit PDE4 and strongly stimulates the production of IL-10. Interestingly, the first group is effective against ENL and the second group may also be candidates for the treatment of the reversal reaction. These drugs are not only nonteratogenic but may also exhibit a noteworthy lack of somnolence, constipation and neuropathy.

The pathogenesis of Lucio's phenomenon (16) is poorly understood and effective therapeutic approaches have not yet been clearly defined. Mild cases appear to respond to MB drug therapy. In severe cases, high doses of prednisone are used. Thalidomide has no effect on this type of reaction. At the United States Public Health Service Hospital in Carville, Louisiana, severe cases unresponsive to high doses of steroids have been treated with immunosuppressive cytotoxic drugs such as imuran and cyclophosphamide with or without plasmapheresis, with questionable results. Like burn patients, these patients require intensive wound care, debridement and electrolyte, protein and secondary infection monitoring. Secondary infections, especially Gram-negative infections, require appropriate antibiotic therapy and severe anemia requires transfusions.

Immunotherapy

Antileprosy vaccination can be immunoprophylactic or immunotherapeutic. The goal of immunoprophylaxis is to restore the host's recognition of shared mycobacterial antigens to promote a Th1 response, induce CD8 cytotoxic cells and downregulate the population of T-cells producing IL-4 and IL-5. The aim of immunotherapy is to switch off the mechanism leading to immunopathological damage and increase intracellular mechanisms by which bacilli are killed. Mycobacterial vaccines have been shown to provide some protection against leprosy. Hopefully, appropriate immunotherapy through stimulation of cell-mediated immunity will reduce the large pool of dead organisms and the small population of viable organisms, the so-called persisters. Among the vaccines currently being assessed are the ICRC (Indian Cancer Research Center) bacillus, BCG plus killed *M. leprae*, BCG vaccine alone and *Mycobacterium w*. When these vaccines have been used with MDT, a faster killing of the bacilli, a reduction in the incidence of reactions and a faster attainment of smear negativity have been reported. Because of the relative efficacy of MDT and the potential for further improvement with the utilization of new bactericidal drugs, as well as the operational magnitude of a vaccination program and its cost, immunoprophylaxis and/or immunotherapy appears to be impractical at this time. However, if a vaccine is developed that is effective against both tuberculosis and leprosy, its use could be medically and economically very practical and acceptable in areas highly endemic for tuberculosis and leprosy (36-38).

Conclusions

Among the communicable diseases, leprosy remains one of the leading causes of permanent physical disabilities worldwide. The elimination program for leprosy is aimed at reducing the prevalence to less than 1 case per 10,000 population, which hopefully will lead in due time to a reduction in the transmission of the disease to insignificant levels. However, if this fails, the possibilities of extrahuman reservoirs of *M. leprae*, such as animals, vegetation and soil, and of human subclinical infection as sources of contamination and transmission warrant further investigation (5).

Treatment of nonreactive disease consists not only of chemotherapy but also the management of potential complicating reactions, monitoring and treating peripheral neuritis and ocular involvement, preventing and minimizing physical disability, patient education and social and economic rehabilitation.

Among the problems associated with the present therapeutic regimens are their duration, the adverse effects of clofazimine, the weak bactericidal activity of clofazimine and dapsone, and the failure thus far of current regimens to impact on the incidence of the disease.

Combinations of more potent bactericidal drugs may permit the use of new therapeutic regimens of shorter duration for both PB and MB patients. Because of the tremendous difference in the bacterial load between PB and MB disease, the duration of a future common regimen will need to be a compromise between being possibly too long for PB and too short for MB disease; consequently, the duration could probably be between 3 and 6 months. Due to relapses with current therapeutic regimens, especially in patients with a bacterial index of 4 or greater and in PB patients who have involvement of several nerve trunks, patients need to be followed for at least 5-8 years after stopping therapy.

The WHO Expert Committee on Leprosy contended that thalidomide controls neuritis, relieves the pain and improves nerve function, and acts faster than corticosteroids in ENL reactions. Celgene has developed new analogues of thalidomide —CC-4047 (Actimid®) and lenalidomide (Revlimid®)— which have immunomodulating properties. These drugs have proven effective and promising for patients with multiple myeloma, but their use in leprosy has not yet been reported (23).

The enthusiasm for the use of vaccines in leprosy has decreased due to the significant impact of currently available MDT, the potential for a greater impact with the utilization of regimens combining new bactericidal drugs and the prohibitive cost of a worldwide vaccination pro-

gram. However, the potential usefulness of an effective vaccine in highly endemic areas cannot be denied. BCG has proven partially effective in leprosy, but has performed relatively poorly in tuberculosis. The development of genetically improved BCG not only may be beneficial in tuberculosis and address the resurgence of this infection but also may represent a cost-effective method of controlling leprosy. An alternative potentially cost-effective vaccine for leprosy could be a DNA vaccine created from skin test antigens or the appropriate protective *M. leprae* genetic DNA sequence.

Among the therapeutic and control measures needed to eliminate leprosy are: 1) tools for detecting preclinical disease; 2) shorter duration of therapy using drugs with greater bactericidal activity; 3) improvement in the ability to predict and treat reactional episodes; 4) new methods for the detection and treatment of neuritis and ocular involvement; 5) an understanding of the mode and pattern of transmission; 6) establishment of risk factors for infection; 7) the development of a practical and effective vaccine program; and 8) the removal of the stigma of leprosy through widespread education (9).

With the declining prevalence of leprosy and shortened treatment regimens, there is a movement to integrate the treatment of leprosy into general health services, because they should be able to manage the disease without a significant increase in workload and be more cost-effective. In India, where the dismantling of the vertical program for leprosy, including medical specialists, has begun, the dermatologist remains the only qualified leprosy specialist, which makes it imperative that dermatologists keep abreast of the developments in the area of leprosy (23).

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