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Review Article

### MULTI-DRUG REGIMENS FOR TREATMENT OF LEPROSY

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#### ABSTRACT

Leprosy is a chronic disease caused by the bacteria *Mycobacterium leprae* that causes damage to the skin and the peripheral nervous system. The disease develops slowly (from six months to 40 years!) and results in skin lesions and deformities, most often affecting the cooler places on the body (for example, eyes, nose, earlobes, hands, feet, and testicles). Worldwide, two to three million people are estimated to be permanently disabled because of leprosy. India has the greatest number of cases, with Brazil second and Burma third. In 1999, the world incidence of Hansen's disease was estimated to be 640,000. In 2000, 738,284 cases were identified.

In 1981, The World Health Organization (WHO) recommended the use of multi-drug therapy against leprosy, using dapsone, rifampicin and clofazimine. The introduction of this regimen aimed to control primary and secondary resistance to drug monotherapy, to prevent further resistance of *Mycobacterium leprae* developing to other antibiotics and to prevent relapse. Among three drugs, rifampicin is the most important anti-leprosy drug and is included in regimens for both paucibacillary (PB) and multibacillary (MB) patients.

Although, WHO has stated that no toxic effects have been reported in monthly administration, many have reported rifampicin as the cause of cutaneous eruptions, thrombocytopenic purpura, hepatitis, a flu-like syndrome, hemolytic anemia, shock, respiratory insufficiency and acute renal failure.

Clofazimine is most active when administered daily; it is well tolerated and virtually nontoxic in the usual dosage.

Dapsone is very safe in the dosage used in MDT and according to WHO side-effects are rare. The main side-effect is skin allergic reaction, however hemolytic anemia, methaemoglobinemia, jaundice, agranulocytosis, psychotic reactions and 'dapsone syndrome' have also been reported.

In 1997, the WHO Expert Committee stated that 'it is possible that duration of the current MDT regimen for MB leprosy could be further shortened to 12 months without increasing the risk of developing rifampicin Resistance'. Treatment of leprosy with only one anti-leprosy drug may result in Development of resistance to that drug.

This paper reports side-effects attributed to MDT, the frequency and stoppage of the MDT components.

**Keywords:** Leprosy, Drugs Used, Side Effects of Drug Interaction, Overcoming the Side Effects.

#### INTRODUCTION

Leprosy is a chronic disease caused by the bacteria *Mycobacterium leprae*<sup>1</sup> that causes damage to the skin and the peripheral nervous system, identified by G.H.A Hansen in 1873. *Leprae*, a rod shaped bacillus that is an obligate intracellular (only grow inside of certain human and animal cells). *M.leprae* cannot be grown on routine laboratory culture media, so drug sensitivity testing in vitro is not possible. Growth and drug susceptibility testing are done by injecting into animal model.

Two polar types of Lepromatous leprosy (LL) and tuberculoid (TT) with intermediate 4 forms have been reported:

Indeterminate stage- single lesion frequently heals spontaneously.

Tuberculoid leprosy (TT) few skin lesion.

Borderline tuberculoid leprosy (BT)

Borderline leprosy (BB)

Borderline lepromatous leprosy (BL)

Lepromatous leprosy (LL)- most severe stage, diffuse skin lesions and high bacterial load.

Transition toward the tuberculoid leprosy (TT) end of spectrum is referred to as Upgrading (may lead to reversal or type 1 reaction) and transition toward the lepromatous leprosy (LL) pole as downgrading. Tuberculoid leprosy is characterized by normal cell mediated immunity, a positive lepromin skin reaction, granuloma formation and relative

paucity of bacilli. Lepromatous leprosy is characterized by depressed cell mediated immunity numerous bacilli within the tissue, no granuloma and a negative skin test for leproma.

#### CLASSIFICATION

Multibacillary leprosy – either positive smears, at any site or multiple (>5) hypo pigmented, hypo anaesthetic or erythematous skin lesions.

Paucibacillary leprosy – negative smears at all sites, single or only a few hypo pigmented and hypo anaesthetic skin lesion.

#### COMMON DRUGS USED FOR TREATMENT OF LEPROSY

WHO recommend the use of combination of three antibiotic namely Dapsone, Rifampin and Clofazimine which takes six months to a year or more.

In general, paucibacillary leprosy is treated with two antibiotics, dapsone and rifampicin, while multibacillary leprosy is treated with the same two plus a third antibiotic, clofazimine. Usually, the antibiotics are given for at least six to 12 months or more. Each patient, depending on the above criteria, has a schedule for their individual treatment, so treatment schedules should be planned by a clinician knowledgeable about that patient's initial diagnostic classification. Antibiotics can treat paucibacillary leprosy with little or no residual effects on the patient. Multibacillary leprosy can be kept from advancing, and living *M. leprae* can be essentially eliminated from the person by antibiotics, but the damage done before antibiotics are administered is usually not reversible. Recently, the WHO suggested that single-dose treatment of patients with only one skin lesion with rifampicin, minocycline (Minocin), or ofloxacin (Floxin) is effective. Studies of other antibiotics are ongoing. The role for surgery in the treatment of leprosy occurs after medical treatment (antibiotics) has been completed with negative skin smears (no detectable acid-fast bacilli) and is often only needed in advanced cases. Surgery is individualized for each patient with the goal to attempt cosmetic improvements and, if possible, to restore limb function and some neural functions that were lost to the disease. Prevention of contact with droplets from nasal and other secretions from patients with untreated *M. leprae* infection currently is a way to avoid the disease.

#### DAPSONE

Dapsone is a sulfone compound. It is commonly used in combination with rifampin and clofazimine as multi drug therapy for the treatment of *Mycobacterium leprae* infections. It is also second-line treatment for prophylaxis (prevention) against *Pneumocystis pneumonia* (PCP) caused by *Pneumocystis jiroveci* (formerly *P. carinii*) in HIV patients in whom CD4 counts are below 200/mm<sup>3</sup>. To treat acne, Dapsone is marketed as Aczone by Allergan.

#### Mechanism:

As an antibacterial, dapsone inhibits bacterial synthesis of dihydrofolic acid, via competition with para-aminobenzoate for the active site of dihydropteroatesynthetase. Though structurally distinct from dapsone, the sulfonamide group of antibacterial drugs also work in this way.

Dapsone has anti-inflammatory and immunomodulatory effects. Dapsone blocks myeloperoxidase, which has been

suggested to be its mechanism of action in treating dermatitis herpetiformis.

#### Administration:

Dapsone is administered orally as a 100 mg tablet or alternatively as 25 mg tablets. Dapsone is administered transdermally (via the skin) as a gel 5% topical acne medication and available in 3-, 30-, and 60-gram tubes. In normal use, 0.5 grams should be administered to the face per application twice a day.

#### Specific considerations:

Certain patients are at higher risks of adverse effects when using dapsone. Some specific issues that should be considered are:

Related to the blood (a full blood count should be obtained prior to initiating therapy):

- Porphyria
- Anemia
- Cardiac disease
- Pulmonary disease
- HIV infection
- G6PD deficiency
  - Related to the liver (obtain liver Function tests before starting therapy):
- Liver impairment
  - Related to allergy:
- Sulfonamide allergy is associated with dapsone allergy.<sup>16</sup>

#### CLOFAZIMINE

CLOFAZIMINE is a fat-soluble riminophenazine dye used in combination with rifampicin and dapsone as multidrug therapy (MDT) for the treatment of leprosy. It has been used investigationaly in combination with other antimycobacterial drugs to treat *Mycobacterium avium* infections in AIDS patients and *Mycobacterium avium* paratuberculosis infection in Crohn's disease patients. Clofazimine also has a marked anti-inflammatory effect and is given to control the leprosy reaction, erythema nodosum leprosum (ENL). Drug is given as an alternative to patients who cannot tolerate the effects of dapsone for tuberculosis.

#### Mechanism:

Clofazimine works by binding to the guanine bases of bacterial DNA, thereby blocking the template function of the DNA and inhibiting bacterial proliferation. It also increases activity of bacterial phospholipase A<sub>2</sub>, leading to release and accumulation of lysophospholipids, which are toxic and inhibit bacterial proliferation.

#### Administration:

Clofazimine is available in gelatin capsules of 50 and 100 mg. The adult dose is 50 mg daily or 100 mg twice weekly and for children 1 mg/kg. Due to its long tissue half-life, administration of the drug can be adapted, such as the WHO recommended scheme of 50 mg/day supplemented by 300 mg once a month.

#### Immunosuppressive effects

The immunosuppressive effects of clofazimine were immediately noticed when applied in animal model. Macrophages were first reported to be inhibited due to the stabilization of lysosomal membrane by clofazimine. Clofazimine also has been sporadically reported with some success in other autoimmune diseases such as psoriasis,

Miescher's granulomatous cheilitis, Crohn's disease and ulcerative colitis. A recent clinical study of clofazimine was done in post-bone marrow transplantation patients with over 50% of them having skin involvement, flexion contractures or oral manifestations achieved complete or partial responses. 7 out of 22 patients were able to reduce other immunosuppressants such as cyclosporine A<sup>17</sup>.

#### RIFAMPICIN

RIFAMPICIN (INN) (or rifampin (USAN)) is a bactericidal antibiotic drug of the rifamycin group. It is a semisynthetic compound derived from Amycolatopsisrifamycinica (formerly known as Amycolatopsis mediterranei and Streptomyces mediterranei). There are various types of rifamycins from which this is derived but the rifampicin form, with a 4-methyl-1-piperazinamyl group, is by far the most clinically effective. Rifampicin is used in the treatment of a number of bacteria, but best known for activity against Mycobacterium strains, such as cause tuberculosis and Hansen's disease. Rifampicin can be used as monotherapy for a few days as prophylaxis against meningitis, but resistance develops quickly during long treatment of active infections, so the drug is always used against active infections in combination with other antibiotics.

#### Mechanism:

Rifampicin inhibits DNA-dependent RNA polymerase in bacterial cells by binding its beta-subunit, thus preventing transcription to RNA and subsequent translation to proteins. Its lipophilic nature makes it a good candidate to treat the meningitis form of tuberculosis, which requires distribution to the central nervous system and penetration through the blood-brain barrier. Rifampicin-resistant bacteria produce RNA Polymerases with subtly different  $\beta$  subunit structures which are not readily inhibited by the drug.

#### Administration:

Rifampicin is usually administered in a single daily dose of 10 mg/kg, 600 mg in adults and 450 mg in persons weighing less than 35 kg. Due to its marked bactericidal activity, rifampicin can be used intermittently, with doses ranging from 600 to 1200 mg and at intervals ranging from 1 week to 1 month.

#### Interactions:

Rifampicin is an inducer of many enzymes of the cytochrome P450 superfamily, including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, and CYP3A7. Thus it will speed up the metabolism of any drug that is metabolized by any of these enzymes in the body. A complete list of drugs metabolized by each of these enzymes can be found here. Other possible interactions which may not be listed include antiretroviral agents, everolimus, atorvastatin, rosiglitazone/pioglitazone, celecoxib, clarithromycin, caspofungin, and lorazepam.

#### ETHIONAMIDE (2-ethylthioisonicotinamide, Treacor SC)

Ethionamide is an antibiotic used in the treatment of tuberculosis. It is a prodrug. It has been proposed for use in combination with gatifloxacin. The action may be through disruption of mycolic acid.

#### MINOCYCLINE (INN)

Minocycline is a broad-spectrum tetracycline antibiotic, and has a broader spectrum than the other members of the group. It is a bacteriostatic antibiotic, classified as a long-acting type.

As a result of its long half-life it generally has serum levels 2–4 times that of the simple water-soluble tetracyclines (150 mg giving 16 times the activity levels compared with 250 mg of tetracycline at 24–48 hours). Minocycline is not a naturally occurring antibiotic, but was synthesized semi-synthetically from natural tetracycline antibiotics by Lederle Laboratories in 1972, and marketed by them under the brand name Minocin.<sup>19</sup>

#### CLARITHROMYCIN

Clarithromycin is a macrolide antibiotic used to treat pharyngitis, tonsillitis, acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, pneumonia (especially atypical pneumonias associated with Chlamydia pneumoniae or TWAR), skin and skin structure infections. In addition, it is sometimes used to treat Legionellosis, Helicobacter pylori, and Lyme disease.

#### Mechanism

Clarithromycin prevents bacteria from growing by interfering with their protein synthesis. Clarithromycin binds to the subunit 50S of the bacterial ribosome and thus inhibits the translation of peptides. Clarithromycin has similar antimicrobial spectrum as erythromycin but is more effective against certain gram-negative bacteria, particularly Legionella pneumophila. Besides this bacteriostatic effect, clarithromycin also has bactericidal effect on certain strains such as Haemophilus influenzae, Streptococcus pneumoniae and Neisseria gonorrhoeae.

#### Contraindications

Clarithromycin should be used with caution if the patient has liver or kidney disease, certain heart problems (e.g., QT prolongation or bradycardia), or an electrolyte imbalance (e.g., low potassium or magnesium levels). Many other drugs can interact with clarithromycin, which is why the doctor should be informed of any other drugs the patient is taking concomitantly. Clarithromycin is almost never used in HIV patients due to significant interaction with HIV drugs. Clarithromycin should not be used in pregnant patients. Clarithromycin can also cause serotonin syndrome symptoms when taken in conjunction with buspirone (Buspar).

#### SIDE EFFECTS DUE TO ANTI-LEPROTIC DRUG INTERACTIONS

Laboratory assessments were done before the start of MDT and between 30–90 days of the treatment. Tests included hemogram and liver function tests. Level of methemoglobin was only requested when there was clinical suspicion of methemoglobinemia. Side-effects attributed to MDT were defined as the presence of undesirable secondary effects of onset after the start of MDT.

- ❖ **Hemolytic anemia** was defined as a reduction of hemoglobin from baseline to the end of 30–90 days (less than 12.7g/dL for men and 11.5 for women), and reduction of hematocrit (less than 42% for men and 36% for women). Symptoms like fatigue, weakness, shortness of breath, jaundice, enlarge of spleen, or/and abdominal discomfort may be present.
- ❖ **Leucopenia** was defined as a reduction in the number of circulating leucocytes in the blood less than 4,500/ml.
- ❖ **Methemoglobinemia** was defined as raised level of methemoglobin in the blood more than 1%; shortness of breath, cyanosis, mental status changes, headache,

fatigue, dizziness, loss of consciousness, dysrhythmias, seizures, coma and death may occur.

- ❖ **Psychiatric disorders** was defined as mood, psychotic and anxiety disorders. All patients with suspected psychiatric disorders were reviewed by a psychiatrist.
- ❖ **Gastrointestinal manifestation** was defined as the presence of dysphagia, or dyspepsia, nausea, diarrhea, vomiting and bleeding (hematemesis, melena or hematochezia).
- ❖ **Hepatic abnormalities** were defined as any alterations at liver function tests with or without clinical evidence of jaundice, malaise and other symptoms.
- ❖ One or more of these had to be present: Serum aminotransferases, gamma-glutamyltranspeptidase and alkaline phosphatase were defined as abnormal when they were twice the upper limit of normal. Total bilirubin more than 1.2mg/dL. Dizziness was defined as one or more of these: Faintness, light-headedness, loss of balance, sense of spinning, and vague spaced-out feeling.
- ❖ **Hypersensitivity reaction** was defined as one or more of these: Watery, itchy eyes, runny nose, rashes, itchy skin, sneezing, swelling in small areas of the skin and angioedema.
- ❖ **Anaphylactic reaction** was defined as a recent onset (1 minute to 1 hour after taking MDT) of the most of these: palpitations, low blood pressure, fainting, tingling sensations, itchy and flushed skin, throbbing in the ears, coughing, sneezing, hives, angioedema, and wheezing.
- ❖ **Flu-like syndrome** was defined as the most of these: Fever, runny nose, sore throat, cough, nausea, vomiting, poor appetite, headache, muscle/joint aches, and malaise.
- ❖ **Skin reactions** were defined as the following: Skin rashes or exanthematous eruption which may be localised or generalised; exfoliative dermatitis (exfoliation extending to over 90% of the body surface area including the scalp and fever); toxic epidermal necrolysis causing several large flaccid blisters extending over the entire skin surface except the scalp, malaise and fever may be present. Stevens-Johnson syndrome or erythema multiforme bullosum in which the skin and oral mucosa are always involved and eyes may be sometimes involved, fever and prostration.
- ❖ **Sulfone syndrome** was defined as an exfoliative dermatitis and/or other skin rashes, generalised lymphadenopathy, fever, hepatosplenomegaly and hepatitis occurring within 6 weeks of starting therapy. Data on skin discoloration and ichthyosis attributed to clofazimine were not collected here. All patients completed leprosy treatment and were considered 'cured'.

#### Leprosy reactions

About half of leprosy patients experience acute episodes of destructive inflammatory reactions caused by their immune response to bacterial antigens released when bacilli die. Reactions may occur before, during and even after completion of therapy. It is very important to continue antimicrobial therapy while giving immunosuppressive therapy during these reactional states. Most reactions fall under two categories:

Reversal (also known as Type 1, RR, or T1R), and erythema nodosum leprosum (also known as Type 2, ENL, or T2R).

Although distinct conditions, they may arise at different times in the same patient. Leprosy reactions can result in permanent loss of nerve function; that is, a reduction in sensory or motor function.

#### Reversal reaction:

Reversal reactions (T1Rs) are a delayed hypersensitivity immune system response that develops after exposure to an antigen that the immune system recognizes as foreign. T1Rs in leprosy occur most often during the first 6 months of MDT in patients with either PB or MB leprosy, but more commonly in MB. Clinically, a T1R is characterized by inflammation within skin lesions or within nerves or both. A pre-existing skin lesion may abruptly become oedematous and erythematous, which can lead to ulceration. T1Rs can reoccur, which increases the risk of nerve damage. Treatment of T1Rs consists of anti-inflammatory drugs such as corticosteroids, aimed at preventing tissue destruction and nerve damage. The drug interaction between prednisone and rifampin is significant, and rifampin dosage should decrease from 600 mg/day to 600 mg/month with the addition of corticosteroid therapy.<sup>34</sup>

#### Erythema nodosum leprosum:

Erythema nodosum leprosum (ENL) occurs in BL and LL leprosy and is a serious and often prolonged immunological reaction. It is mediated by circulating immune complexes, and involves the release of very high levels of tumour necrosis factor (TNF- $\alpha$ ) by peripheral blood monocytes. ENL can be treated with high-dose prednisone, which quickly suppresses the inflammatory state. However, prolonged prednisone use is associated with numerous metabolic side effects, cataracts, hypertension, diabetes mellitus, and aseptic hip necrosis, as well as possible activation of co-infections such as tuberculosis, and a reported case of fatal strongyloides.<sup>35</sup> In 2006, a severe ENL case was treated successfully with the genetically engineered biologic infliximab.<sup>46</sup> However, infliximab is expensive, and can also reactivate infections including unmasking previously undiagnosed cases of leprosy.<sup>36</sup> In 1964, Dr Jacob Sheskin discovered the beneficial effects of thalidomide on suppressing ENL reactions.<sup>37</sup> From the 1970s into the 1990s, while working at Carville, Dr Robert Hastings was the leader in making thalidomide available under an investigational new drug (IND) protocol for the treatment of ENL in the US at a time when it was otherwise banned in the US because of its severe teratogenicity. Thalidomide has a very rapid onset of action in controlling severe ENL and reduces the need for prednisone. In the US, it is now available under the System for Thalidomide Education and Prescribing Safety (STEPS) program's stringent guidelines for use only by physicians who register with the program.<sup>18</sup> The current WHO guidelines for the management of severe ENL include clofazimine but exclude the use of thalidomide;<sup>38</sup> however, much remains to be learned about optimal therapies, dosages, and duration of treatment.

#### Relapses after MDT

The long-term success of any antimicrobial therapy of an infectious disease is usually judged by eradication of the responsible infectious organism. For most human infectious diseases, this means negative culture results and clinical cure. *M. leprae* is unique in that there is no method, to date, of in

vitro culturing. The WHO therefore uses a proxy approach, defining a leprosy relapse case as a patient, who successfully completes an adequate course of WHO MDT, but subsequently develops new symptoms of the disease either during the surveillance period or thereafter.<sup>38, 39</sup> The WHO further defines relapse in MB leprosy as: “*the multiplication of M. leprae suspected by the marked increase (at least 2+ over the previous value) in the bacterial index at any single site, usually with evidence of clinical deterioration.*”<sup>40</sup> Recognition of relapse in paucibacillary leprosy is somewhat difficult as, clinically, PB relapse and PB reversal reactions can be indistinguishable.<sup>40</sup> The WHO advises that: “In theory, a therapeutic test with corticosteroids may be able to distinguish between these two phenomena: a definite improvement within four weeks of corticosteroid therapy denoting reversal reaction, and nonresponse to corticosteroids during the same period favoring the diagnosis of clinical relapse.”<sup>40</sup>

The main differential diagnoses for relapse are reversal reactions, erythema nodosumleprosum and reactivation/resistance/reinfection. The most reliable criteria for making an accurate diagnosis of relapse include clinical, bacteriological, and therapeutic criteria. Additional ones that may be used, depending on the setting, are histopathological and serologic criteria.<sup>37</sup>

The first WHO MDT guidelines, adopted in 1982, included supervised monthly rifampin and clofazimine and daily unsupervised dapsone and clofazimine given for 2 years for MB leprosy.<sup>41</sup> However, in 1998, WHO guidelines reduced the standard course of MDT treatment of MB disease to 1 year, and also eliminated the requirement for bacteriological assessment, including slit skin smears and histology for bacteriological assessment.<sup>24</sup> This made follow-up for relapse of those diagnosed post-1998 more difficult, since some cases may have been originally misdiagnosed,<sup>28</sup> or bacterial indices not measured.

Relapsed cases of leprosy should be identified and placed back on chemotherapy as soon as possible to prevent further disability and transmission of infection. Factors that should be considered in choosing an appropriate regimen are the type of leprosy (PB or MB), previous treatment and drug resistance. Occasionally, clinicians may need to use their judgment to modify the standard WHO treatment regimens according to the scenario in each patient.<sup>42</sup> WHO guidelines<sup>35</sup> are that all MB cases should be treated with standard MB-MDT without waiting for results of drug resistance studies, and that MB-MDT treatment should be continued accordingly (clofazimine 50 mg, ofloxacin 400 mg, and minocycline 100 mg daily for 6 months) even if dapsone resistance is detected; but if rifampin-resistant *M. leprae* are present, or both dapsone and rifampin resistance are present, then this same combination of drugs (clofazimine 50 mg, ofloxacin 400 mg, and minocycline 100 mg daily) should be continued for another 18 months or a total of 24 months.

Relapse rates post-2 year WHO MDT of MB leprosy in three prospective studies have varied from 0% to as high as 20%, with the highest risk being for those who had a pre-MDT average BI of 4 or above. A prospective study published in 2009 showed a relapse rate cumulative risk of 6.6% in 500

MB patients, who were first enrolled between 1987 and 1994, and were followed at a well-established leprosy referral and treatment center, Cebu City Clinic, Philippines, for 6–16 years (mean 10.5 years) post-completion of 2 years of WHO MDT, with those with a pre-MDT BI of 4 or above having a cumulative risk of 10.1%.<sup>42</sup> In mouse footpad assays, *M. leprae* from relapsed patients were rifampin and clofazimine sensitive, and combined with the complete data set, the results suggested that relapses were due to activation of dormant *M. leprae* (persisters) not killed by MDT, rather than new infections.<sup>42</sup>

There is a concern that, especially for patients with BIs of 4 or above, the 1998 reduction of the WHO MDT for MB leprosy from 2 years to 1 year may lead to increased numbers of relapses.<sup>42</sup> The same may be true for PB cases whose treatment times were also reduced to 6 months in 1998.

Methods of detecting drug resistance are being replaced by molecular detection methods of mutations in the *rpoB* gene for rifampin resistance, *folP1* for dapsone resistance, and *gyrA* for ofloxacin resistance. In a recent Brazilian study,<sup>44</sup> 145 relapse cases were studied for MDT drug resistance through gene sequence analysis, with 92 cases having successful positive amplification of genes associated with *M. leprae* drug resistance. Of the 92 cases, four cases, (three MB cases post-2 year MDT and one PB case post-1 year MDT) showed gene mutations suggesting drug resistance. One analysis indicated resistance to rifampin and those of three relapsed cases indicated multidrug resistance: to both dapsone and rifampin in one case, and in two cases (including the relapsed PB) mutations for three drugs: dapsone, rifampin, and ofloxacin. The median time from end of MDT to relapse was 9.45 years for all relapsed cases, but with a significantly shorter median time to relapse of 3.26 years (range: 1 month to 6.6 years) in those cases showing mutations for drug resistance.<sup>44</sup>

#### OVERCOMING SIDE EFFECTS

WHO stated alternative treatments can be given to patients who do not tolerate MDT due to adverse reactions or contraindications, but first of all it is very important to establish conclusively that the adverse reactions noticed are due to the anti-leprosy drugs. Once this is established, other new anti-leprosy drugs can be tried.

Alternative regimens should be administered under direct supervision in a referral centre:

Daily administration of 50mg of clofazimine, together with 400mg of ofloxacin and 100mg of minocycline for 6 months; followed by daily administration of 50mg of clofazimine together with 100mg of minocycline or 400mg of ofloxacin for at least an additional 18 months could be used to replace rifampicin in adult MB patients.

For PB patients, dapsone may be substituted by clofazimine in the same dosage as that used for MB patients during 6 months. For MB patients, dapsone should be stopped and treatment continued with rifampicin and clofazimine in the standard dosage.

Patients who do not accept clofazimine can be treated with a monthly administration of a combination consisting of 600mg of rifampicin, 400mg of ofloxacin and 100mg of minocycline (ROM) for 24 months.<sup>3</sup> Surprisingly, despite the importance of this subject, no other similar studies have been published

and the current literature describes the frequency of MDT interruption as a very scarce event. The difference in rate of side-effects attributed to MDT may be due to ethnic, genetic differences in the Brazilian population. In conclusion, side-effects necessitating treatment stoppage may be more frequent than previously described. There are important issues to discuss such as when to stop drugs. Alternative drugs active against *M. leprae* should be available to the Leprosy Control Programme.

#### New drug treatments

Three US Food and Drug Administration (FDA)-approved antimicrobial drugs – moxifloxacin, gatifloxacin, and linezolid – were tested in mouse footpads for bactericidal effect against *M. leprae*. They were evaluated alone and in combination with the rifamycins – rifampicin (rifampin) and rifapentine – to simulate a MDT regimen. All three were found bactericidal against rapidly multiplying *M. leprae*<sup>52</sup>.

Moxifloxacin is an FDA-approved fluoroquinolone antimicrobial drug that carries a risk of tendinitis and tendon rupture, especially in those over age<sup>50</sup>. It is considered a drug of last resort when all other antibiotics have failed. In clinical trials for drug-resistant tuberculosis, a single dose of moxifloxacin of up to 800 mg was tolerated well, but some patients experienced major adverse events (nausea, vomiting, muscle pain, tremors, insomnia, and dizziness) after 6 months' continual use of 400 mg once daily<sup>52</sup>.

Gatifloxacin is a FDA-approved fluoroquinolone antibiotic that inhibits the bacterial enzymes DNA gyrase and topoisomerase IV. In clinical trials for drug-resistant tuberculosis treatment, a single dose of gatifloxacin (400 mg) was tolerated well. Patients treated with gatifloxacin at 100 to 400 mg/day for 5 to 12 days reported only mild adverse events<sup>52</sup>.

Linezolid is a synthetic oxazolidinone drug approved by the FDA to treat infections by Gram-positive bacteria. It is a protein synthesis inhibitor, stopping the growth of bacteria by disrupting their production of proteins. Long-term use (more than two weeks) can cause bone marrow suppression and low platelet counts, and continual long-term use can cause peripheral neuropathy, optic nerve damage, and lactic acidosis. In several clinical trials for drug-resistant tuberculosis, with daily linezolid doses averaging 600 mg, more than 61% of patients reported adverse events, and more than 36% discontinued linezolid due to adverse events.<sup>52</sup>

#### Vitamin D

In order for host-adaptive immune system T-cells to fight off infection from *M. leprae*, immature T-cells must first be exposed to traces of the foreign pathogen, which happens once they are presented by macrophages with suspicious “cell fragments” or “traces” of the bacillus. The T-cells subsequently divide and multiply into hundreds of identical cells that are all focused on the same pathogen type, leading to a targeted immune response. Professor Carsten Geisler recently found how vitamin D is involved in this adaptive T-cell activation: once an immature T-cell is presented with a foreign pathogen, it extends a vitamin D receptor (VDR), which searches the vicinity for vitamin D. If vitamin D is present, it binds with the VDR, returns to the T-cell nucleus, and activates the gene that initiates transformation to a mature

immune cell. This means that if the nascent T-cells cannot find enough vitamin D in the blood, they won't even begin to mobilize<sup>53</sup>.

T-cells that successfully activate transform into one of two types of immune cell. They either become killer cells that attack and destroy all cells carrying traces of a foreign pathogen, or they become T helper type 1 cells (Th1) that assist the immune system in acquiring “memory.” The Th1 cells send messages to the immune system, passing on knowledge about the pathogen so that the immune system can recognize and remember it at their next encounter.

Recently researchers compared the micro-RNAs (miRNA) in human skin lesions from two types of leprosy, tuberculoid (T-Lep) and Lepromatous (L-Lep) (see Table 1). MiRNAs are small molecules made up of ribonucleic acids that do not code information for proteins, but rather they bind to the RNA that does code for proteins and block them. The researchers found that *M. leprae* can actually regulate the host's cellular miRNA profile at the site of the infection to interfere with the antimicrobial response.<sup>64</sup> Human monocytes, or macrophages, infected with *M. leprae* express the miRNA, hsa-mir-21 which actually blocks the nascent T-cell's gene that would otherwise activate when vitamin D is present, preventing the transformation into Th1 cells.

With this discovery, the researchers recognized a potential therapeutic approach that doesn't rely on administering drugs toxic to *M. leprae*, but rather administering anti-hsa mir-21 to help counter the overexpression of hsa-mir-21 induced by *M. leprae*, together with vitamin D supplementation.<sup>54</sup> This combination, at the proper dose, should encourage a strong adaptive immune response, to limit or even heal the *M. leprae* infection.

## DISCUSSION

Leprosy or Hansen's disease (HD) is a chronic disease caused by the bacteria *Mycobacterium leprae* and *Mycobacterium lepromatosis*. Named after physician Gerhard Armauer Hansen, leprosy is primarily a granulomatous disease of the peripheral nerves and mucosa of the upper respiratory tract; skin lesions are the primary external sign. Left untreated, leprosy can be progressive, causing permanent damage to the skin, nerves, limbs and eyes.

Contrary to folklore, leprosy does not cause body parts to fall off, although they can become numb or diseased as a result of secondary infections; these occur as a result of the body's defenses being compromised by the primary disease. Secondary infections, in turn, can result in tissue loss causing fingers and toes to become shortened and deformed, as cartilage is absorbed into the body. Although the mode of transmission of Hansen's disease remains uncertain, most investigators think that *M. leprae* is usually spread from person to person in respiratory droplets. Studies have shown that leprosy can be transmitted to humans by armadillos.

MDT for multi bacillary leprosy consists of rifampicin, dapson, and clofazimine taken over 12 months. Dosages adjusted appropriately for children and adults are available in all primary health centres in the form of blister packages. Single dose MDT for single lesion leprosy consists of rifampicin, ofloxacin, and minocycline.

In an research it was found that Eighty-eight - almost half - of the 194 studied patients had at least one side-effect attributed to at least one MDT component. Dapsone caused most of the side-effects. However 40% had side-effects due to more than one of the studied drugs. Half of the patients, who had side-effects, had more than one side-effect.

## CONCLUSION

Complete control of leprosy or any infectious disease is possible if the cycle of transmission is broken in endemic areas with a highly effective vaccine. Until this happens, a simplified, accurate diagnostic test for both *M. leprae* and *M. lepromatosis* would help shorten the time for leprosy patients to start MDT. Educational efforts should continue to help reduce and remove the stigma associated with a leprosy diagnosis, and help reduce noncompliance with MDT that leads to drug resistance.

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