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Treatment of leprosy

Hemanta Kumar Kar, MD*, Ruchi Gupta, MD

Department of Dermatology, STD, and Leprosy, PGIMER & Dr RML Hospital, New Delhi, 110001, India

Abstract Leprosy is a curable disease, having been eliminated from many countries, including India. This has been possible due to the wide availability of effective and safe drugs. Treatment of leprosy has undergone considerable changes over decades, from chaulmoogra oil in 1915 to dapsone monotherapy in 1946, then eventually to multidrug therapy (MDT) in 1982. In the last two decades, reports of resistance to all first-line drugs have appeared in the literature, with the need to conduct clinical trials using newer but highly bactericidal drugs and their combinations against *Mycobacterium leprae*.

Introduction

Leprosy plays a significant role in development of disabilities and deformities seen in the world's population. Despite its elimination from a large part of the world, leprosy remains an important health problem, especially in major endemic countries like India and Brazil.[1] Since the introduction of multidrug therapy (MDT) in 1982, spectacular success has been achieved in reducing the disease burden; it has helped not only in reducing the duration of treatment but also in addressing the problems related to resistance to antileprosy drugs, relapses, and disabilities. MDT is not invulnerable to poor compliance (related to long duration and other socioeconomic factors) and drug resistance.[2] There has been a renewed effort to find newer regimens that may further shorten the duration of therapy and improve compliance, while simultaneously maintaining or improving the therapeutic advantages of previous regimens.

* Corresponding author. Tel.: 9868506372.
E-mail address: hkkar_2000@yahoo.co.in (H.K. Kar).

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First-line drugs

The backbone of current treatment of leprosy is formed by MDT consisting of dapsone, clofazimine, and rifampicin. Detailed descriptions of individual drugs are given here and their pharmacokinetics are summarized in Table 1.

Dapsone (4,4-diaminodiphenylsulfone)

Before the introduction of dapsone as a therapeutic option for leprosy in 1946 by Guy Faget,[3] intradermal injection of chaulmoogra or hydnocarpus oil (derived from seeds of an herbal tree) and its esters with weak antileprotic property were the mainstay of treatment of leprosy.[4]

Dapsone is a bacteriostatic drug that acts by competitive inhibition of the enzyme—dihydrofolate synthetase and dihydrofolate reductase, key enzymes in the folate biosynthesis pathway in *M leprae*.[5] In patients on dapsone monotherapy, the killing of bacilli was complete in 3 to 6 months, and complete clinical regression usually takes around 2 to 3 years. As with all antileprosy medication, mucosal lesions are first to heal, resulting in clearing of nasal passages, subsidence of epistaxis, and decrease in foul smell from the nose, followed by skin ulcers, whereas regression of nodules and skin thickening

Table 1 Pharmacokinetics of various chemotherapeutic agents

Drug	Absorption	Metabolism	T1/2	Excretion	MIC (μg/ml)	Peak serum level (PSL) achieved	No. of days for which PSL achieved exceed MIC	Dose (mg/kg)
Dapsone	99%, PSL [a] are reached in 4-6 hrs	Acetylation and N-hydroxylation in liver [b]	28 hr	Feces	0.03	0.4-1.2 mg/ml (500-600 times MIC)	10	1-2 mg/kg (100)
Acedapsone	PSL in 1 wk	Same	-	Feces	0.03	8 times MIC	200	225 mg once in 11 weeks.
Rifampicin	90%, Better in empty stomach, PSL in 2-3 hr	De-acetylation and oxidation in liver	12 hr	35% in urine & 65% in feces	0.3	6-8 μg/ml (45-70 times MIC)	1	10 mg/kg (600)
Clofazimine	30%-50%	Kidney: one conjugated and two unconjugated metabolites. one by hydrolytic dehalogenation & 2nd by hydrolytic deamination followed by glucuronidation	60 days	1% in Urine	-	50 mg -0.5 μg/ml 300mg-1.0 μg/ml	-	50 mg (daily) 300mg (MSD)
Clarithro-mycin	50%	Liver: 14-hydroxy Clarithromycin [c] is almost twice as active.	5-7 hrs	Both urine and feces	0.125	10 times MIC	-	500mg/d (12.5 mg/kg)
Minocycline	95%-100%, not affected by meals	Liver: 9-hydroxyMinocycline	15-23 hrs	Feces	0.2	10-20 times MIC	-	100mg/d
Ofloxacin	98%, PSL in 1-3 hr	metabolized predominantly by the liver	4-5 hr	Excreted by kidney	-	-	-	500mg/d

[a] Peak serum levels.

[b] Dapsone is acetylated polymorphically that is, some patients rapidly acetylate dapsone to monoacetyldapsone (MADDS) whereas in others, this process occurs slowly; however, in all patients, MADDS is rapidly de-acerylated. Thus, equilibrium between MADDS and Dapsone is quickly reached and sustained. Dapsone's efficacy and half life appear unrelated to the rate of acetylation. The more clinically significant metabolic pathway involves hydroxylation of one of the amino groups by cytochrome 3A4 (and, to a lesser extent, 2C9) to form Dapsone hydroxylamine, a potent oxidant that is important in the development of methemoglobinemia and hemolysis.

[c] Adjustment of dosage is not necessary in patients with impaired renal function.

starts later. Nerve thickening, sensorimotor loss, and trophic ulcers respond very slowly and often incompletely. The eyes and extremities need special care and protection from trauma and burns.[5] Although well tolerated, dapsone does have some well-known side effects (Table 2).

It was a boon to leprosy patients that was soon clouded by emergence of dapsone resistance in 1960 (Table 3). To overcome this threat and to improve treatment efficacy, in 1982 the World Health Organization (WHO) recommended MDT for leprosy, consisting of concomitant use of two or three drugs in treatment of leprosy.

Rifampicin

Rifampicin, the only bactericidal component of MDT against *M leprae*, was introduced in 1970. It acts by selective inhibition of bacterial DNA-dependent RNA polymerase and blocks RNA synthesis.[6] The drug is also effective against dapsone-resistant organisms. Rifampicin crosses the cell membranes and is effective in killing intracellular organisms. The morphologic index (MI) comes to zero within 4 to 6 weeks of treatment; however, bacteriologic index (BI) takes longer to decline. A single dose of 1500 mg or 3 to 4 daily doses of 600 mg of the drug given to patients appear to kill more than 99.99% of the viable *M leprae*, as tested in the mouse footpad. Based on the earlier reports, the WHO study group recommended 600 mg once-monthly supervised doses to adults. Side effects (Table 2) are rare with once-a-month dosage. Unfortunately, the exciting usefulness and benefit were soon superseded by emergence of resistance caused by mutation in the Rpo B gene (Table 3).

Clofazimine

Clofazimine is a brick red, fat-soluble crystalline dye with bacteriostatic and antiinflammatory action, whose biochemical basis for antimicrobial actions remains to be elucidated. The drug possibly acts by blocking the template function of DNA, by increasing lysosomal enzyme synthesis, and by increasing phagocytic capacity of macrophages.[7] It binds preferentially to