



REVIEW ARTICLE

Therapy of Leprosy- Present Strategies and Recent Trends with Immunotherapy

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Abstract

Leprosy is a complex infectious diseases cause by *Mycobacterium Leprae*. As the nation is passing through the eradication phase of leprosy, reports are suggesting a change in epidemiology and symptomatology of the disease. Current therapeutic strategies like multidrug therapy (MDT) although effective in treating the majority of cases but not sufficient to eradicate still the new leprosy cases alone and with the complication of diseases like deformities, relapses, and recurrence of cases are occurring in the society. For eradication, there is a requirement of modification of current treatment strategies. The current management of patients affected with leprosy is insufficient to prevent nerve disabilities and control relapses, reactions, and recurrences. The need for newer anti-leprosy agents has been felt for a complete cure without complications and deformities. Various agents like fluoroquinolones (FQs), macrolides, and minocycline have also been tried in various combinations and duration. We reviewed the various issues related to treatment, drug resistance, and the possible steps of complete eradication of this stigmatized disease from the world. While alternative chemotherapy or supplemental immune therapies that would offer shorter or easier treatment regimens appear to be feasible, only a small number of trials are performed. More proactive strategies appear necessary in the drive for eradication. This article also reviews the addition of an immunotherapeutic strategy against leprosy.

Keywords

Leprosy, MDT, Chemotherapy, Immunotherapy, MIP, ROM

Introduction

Defamation of all and their negative perception of leprosy negatively affect the mental well-being of pa-

tients, and often give patients the feeling of stigma. Leprosy, perhaps the most serious human illness identified by Gerhard Armer Hansen of Norway in 1873, is still a major issue in many parts of the world, which mainly affects the skin and peripheral nerves, but may also affect the muscles and other parts of the body [1].

The global leprosy situation has improved dramatically over the last four decades since the implementation of MDT in 1982, with a decrease in prevalence from more than 5 million cases in the mid-1980s to less than 200,000 at the end of 2016. Although the prevalence of this disease has decreased significantly and most historically highly endemic countries have achieved elimination (defined as the recorded prevalence rate of < 1 case/10000 population), it remains a global health concern [2]. There is no highly successful or precise cure available for leprosy, hence the various types of treatment have been used. Newer, more efficient, and also operationally fewer demanding regimens are needed to further reduce the duration of treatment, especially in multi-bacillary (MB) patients. After completion of therapy, the frequency of "reactions" and "relapses" must be minimized. Besides, it would be very beneficial if the same therapy plan with different durations of time could be provided to both patients with paucibacillary (PB) and MB [3]. The evaluation of the function of immunotherapy and immune-prophylaxis would also help to eradicate the disease.



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Table 1: Important achievements in the Leprosy therapy.

Late nineteenth century- until the 1940s	Use of chaulmoogra oil in the treatment of Leprosy [5,6]
1940	Promin, a sulfone drug, was introduced as a treatment for leprosy [7,8]
1941	Dapsone was first used by Faget, et al. for the treatment of leprosy in Carville, Louisiana, USA [3,9]
1955	National Leprosy Control Programme (NLCP) was launched in India to control the number of leprosy infection [10]
1964	The emergence of resistance to dapsone [11]
1970	Identification of Rifampicin as a new and effective anti-leprosy drug [12]
1981	WHO recommended the use of MDT [13]
1983	National Leprosy Eradication Program (NLEP) was launched in India [14]
1983	Introduction of MDT in India
1992	RO ¹ for 28 days (daily) [15]
1994	WHO-MDT (FDT ¹ -24) [16]
1995	ROM-12 for MB, ROM-6 for PB
1996	WHO-MDT (FDT-12 for MB and FDT-6 for PB)
1997	ROM-1 for 1 day (single dose) [17]
2000	WHO calls for the elimination of leprosy [18]
2005	Elimination of Leprosy in India as a public health problem at the national level in December 2005 [19,20]

ROM¹: Rifampin-Ofloxacin-Minocycline; FDT¹: Fixed drug therapy

Treatment Strategies

Before the period of antibiotics, leprosy was treated with chaulmoogra oil (Table 1) extracted from *Hydnocarpus wightiana* seeds. The oil has been used in India as an Ayurvedic drug for the treatment of leprosy and diverse skin conditions. It has also been used in China and Burma. Frederic John Mouat, an educator at the Bengal Medical College, tried oil as an oral and effective specialist in two cases of leprosy and revealed critical enhancements in the 1854 paper. Sir Leonard Rogers (1868-1962) presented sodium hydnocarpate (later promoted as "ALEPOL") for disease treatment, which denoted the start of leprosy control in India [4]. Force and his associates in 1904 to 1907 examined the science of chaulmoogra. Up to 1920, leprosy was altogether exactly treated with chaulmoogra oil and its subordinates. There was no scientific understanding of the leprosy effect of chaulmoogra oil and the nature of this active drug, whether its treatment was leprosy-specific or other diseases. During the same year, Walker and Sweeney released the findings of an inquiry on these issues it was experimentally determined that chaulmoogra oil contains extremely bactericidal substances [5]. It was formerly administered intensively enough to obtain therapeutic results. It was previously administered in the form of crude oil, by mouth. This oil is, however, so nauseous that very few patients will pursue the procedure as long and vigorously as possible to produce therapeutic success and triggers such a severe digestive disorder. Several attempts have been made to avoid digestive disorders and otherwise improve the therapeutic action of the oil. Subcutaneous and intramuscular injections were tried as long ago as 1899 by Tourtoulis-Bey, Cairo,

with some beneficial results but no cures.

First-Line Antibiotics: Dapsone, Clofazimine, and Rifampicin

Dapsone

Dapsone is bacteriostatic and active against a wide range of bacteria and protozoa. The antimycobacterial function of dapsone was demonstrated for the first time in the treatment of tuberculosis in 1940. The modern era of leprosy therapy began in the 1940s, when Dr. Guy Faget of the National Hansen Disease Center in Carville, Louisiana, showed the remarkable effects of Prominin in the treatment of leprosy [7]. It has been found that the progress in leprosy is not accompanied by traditional cellular changes under prominent treatment. Promin (glucosulfone sodium) was the first sulfone to be used in leprosy instead of the parent compound dapsone, as it was considered to be too toxic and had very promising results but had to be administered intravenously. In 1947, Cochrane used 1.25g subcutaneous dapsone twice a week to successfully treat patients with leprosy [4]. In 1951, normal leprosy treatment was oral dapsone, 100 mg daily, which was commonly used as monotherapy in the 1950s and 1960s. The dosage of 100 mg dapsone is weakly bactericidal against *M. Leprae* and active lesions begin to improve after a few weeks of dapsone therapy. Further studies contributed to the development of Diasone (sodium sulfoxone), Promacetin (aceto-sulfone), and a variety of other sulfones that could be administered orally safely. The re-evaluation of dapsone at the end of the 1940s led to a gradual realization that lower, relatively non-toxic doses of dapsone were equally ef-

fective and was perhaps the only leprosy sulfones. Since dapsone is inexhaustible, safe, practically toxic in the dosages used, and can be administered orally, dapsone monotherapy was the standard treatment for leprosy worldwide until the early 1980s and made a major contribution to leprosy management in certain areas.

Resistance to dapsone

Resistance to Dapsone had started to develop two major problems by the 1960s: first, “secondary resistance” or recurrence was identified in patients previously treated with dapsone, then “Primary resistance” was found in patients who had never been subjected to dapsone. Up to 19 percent of patients experienced treatment relapses and drug resistance to dapsone in the 1970s [21]. The first case of resistance to the dapsone was reported in 1964 [11]. Resistance to dapsone is due to mutations of the gene *folP1*, which encodes the synthase of dihydropteroate. This enzyme is a member of folate synthesis [22]. The WHO notes that side effects of dapsone are rare.

A retrospective analysis of 194 patients in Brazil showed that 43 percent had adverse effects related to dapsone [23]. Dapsone hypersensitivity typically begins with fever, pruritus, and dermatitis rash 3-6 weeks after starting the medication. The syndrome can progress to exfoliative dermatitis unless dapsone is stopped immediately. A prospective cohort study conducted by Hong Liu, et al., including 1,512 patients in China, showed adverse reactions in 384 patients during the follow-up period [24]. The occurrence of hypersensitivity to dapsone is estimated at one in several hundred patients but tends to be higher in Chinese patients (0.5 percent -3.6 percent). The existence of the HLA-B*13:01 gene was highly predictive of dapsone hypersensitivity in a Chinese study of 39 patients who experienced dapsone hypersensitivity out of 872 treated with dapsone as part of MDT [25].

Rifampicin

Rifampicin is a member of the rifamycin group and was first used as a tuberculosis treatment, just like all other treatments for leprosy. Rifampicin is the only strongly bactericidal anti-leprosy drug that makes the patient non-infectious within days of initiation of treatment [26]. The drug is also effective against dapsone-resistant organisms. The target for rifampin in mycobacteria is the β -subunit of the RNA polymerase encoded by *RpoB* and blocks RNA synthesis [1]. The first studies supporting the efficacy of rifampicin against susceptible *M. leprae* strains, but also on resistant strains to dapsone, were conducted in 1970 [12].

A daily dose of 600 mg of rifampicin was given to patients enrolled in the first clinical trial but in 1982 the WHO suggested the use of a monthly dose of rifampicin because: “the increased effectiveness of the 600 mg daily dose of rifampicin compared to the 600 mg month-

ly dose” had not been demonstrated and the need to monitor the use of rifampicin because it was more costly at that time [27]. Unfortunately, the exciting usefulness and benefit were soon superseded by the emergence of resistance caused by a mutation in the *Rpo B* gene [28]. While rifampicin resistance was not reported in more than 10 million patients who completed MDT, this could be due to two reasons. (1) Post- MDT monitoring for relapse has been discontinued. (2) Rifampicin susceptibility testing is difficult to carry out. Polymerase chain reaction (PCR)-based DNA sequence analysis of the *RpoB* gene of *M. leprae* was in complete agreement with the susceptibility test in the mouse footpad system [29]. This method may contribute to the diagnosis of 80 percent of resistant rifampicin strains. Secondary rifampicin resistance is likely to be present in patients who have relapsed after MDT has been completed.

Clofazimine

Clofazimine was first used as monotherapy for leprosy in the early 1960s and continued until the mid-1970s. Clofazimine is bacteriostatic and slowly bactericidal against *M. leprae*, similar to dapsone, but the mechanism of its action against *M. leprae* is unknown. The drug may act by blocking the template function of DNA, increasing lysosomal enzyme synthesis, and increasing the phagocytic capacity of macrophages [30]. Although slow to act, resistance to clofazimine is very rarely reported, which possibly could be due to its multiple mechanisms of action.

The main problems with clofazimine are increased skin pigmentation and dryness (ichthyosis) that occur as the drug becomes clinically effective. Pigmentation can also be seen in the cornea as well as in conjunctival and macular areas of the eyes [31]. The discoloration gradually disappears as the medication is removed, as does the ichthyosis on the chin and forearms. Clofazimine crystals may be stored in the intestine and can induce enteropathy [32].

MDT

In 1981, the MDT, dapsone, rifampicin, and clofazimine were recommended by the WHO Studies Group. This cocktail is safe and efficient in convenient blister packages for the monthly calendar. Since 1995 WHO supplies all patients worldwide free MDT [13]. The recommended duration of treatment for MB leprosy is 12 months. Patients presenting with lepromatous leprosy (LL), borderline leprosy (BL), and borderline-borderline (BB) leprosy according to the Ridley and Jopling system are members of this treatment group. The recommended duration of treatment for PB is 6 months (Table 2). The concept of multiple drugs for the treatment of leprosy was based on the estimate that an advanced, untreated lepromatous leprosy patient had about 11 logs of living organisms. The proportion of the drug-resistant mutants that are naturally occurring is calculated at 1

Table 2: Standard multidrug therapy regimens for paucibacillary and multibacillary leprosy in adults and children (WHO).

Clinical presentations	Population	Agents	Dosing regimen	Treatment duration
Paucibacillary leprosy	Adults	Rifampicin Dapsone	600 mg/month 100 mg/day	6 months
	Children	Rifampicin Dapsone	450 mg/month 50 mg/day	6 months
Multibacillary leprosy	Adults	Rifampicin Clofazimine	600 mg/month 300 mg/month and 50 mg/day	12 months
		Dapsone	100 mg/day	
	Children	Rifampicin Clofazimine	450 mg/month 150 mg/month and 50 mg/day	12 months
	Dapsone	50 mg/day		

in 7 logs for rifampicin, and 1 in 6 for dapsone and clofazimine, respectively. Organisms immune to one drug should have a particular mode of action to defend the other drugs in MDT. The risk of mutating resistance to any two medications decreases to 1 for 13 logs with combination treatment, which is marginal [33]. Since its introduction, MDT has not revised much except the duration of treatment. Initially, the duration of MDT treatment was very long (e.g., 24 months or until smear negativity), which resulted in decreased compliance, resistance, and relapse.

Second-Line Agents: Fluoroquinolones, Minocycline, and Clarithromycin

This group of compounds exerts their antimicrobial activity by inhibiting the DNA gyrase subunit (an enzyme that is not affected by any other therapeutic agent in use) by inhibiting the replication of bacterial DNA. Some FQs, such as ofloxacin (OFLO), pefloxacin, sparfloxacin, and moxifloxacin, have all been shown to be effective against *M. leprae* [34]. New anti-leprosy regimens using these drugs have been extensively studied and experience derived from their use in the treatment of leprosy may be used to make use of these drugs as chemoprophylactic agents. Clinical trials have shown that the daily dosage of 400 mg ofloxacin is bactericidal against *M. leprae*, but less than a single dose of rifampicin. Once administered daily at the above dose for 22 days, 99.9 percent of viable species were killed [35]. This category of drugs is well absorbed orally and achieves a peak serum concentration after 2 hours and has a serum half-life of approximately 7 hours. They are excreted largely unchanged by the kidneys. Side effects include nausea, vomiting, other stomach symptoms, and a variety of central nervous system symptoms, including fatigue, headache, dizziness, nervousness, and hallucinations. Severe complications are uncommon and only rarely cause the medication to be discontinued.

In a trial of ofloxacin (OFLO) alone and its combination with dapsone (DDS) and clofazimine (CLF), 24 patients with newly diagnosed LL were allocated randomly to three treatment groups and treated for 56 days by OFLO daily, 800 mg OFLO daily, or 400 mg OFLO combined with 100 mg DDS and 50 mg CLF daily plus 300 mg CLF once every 28 days. The bactericidal activities of the above regimens were measured by titrating the proportion of viable in normal and nude mice. It was estimated that more than 99 percent, > 99.99 percent and, > 99.99 percent of viable *M. leprosy* were killed by 14, 28, and 56 days of diagnosis, respectively. Bacterial activity did not differ significantly between the three groups [36].

Minocycline (7-dimethylamino-6-dimethyl-6-deoxy-tetracycline) is the only member of the tetracycline antibiotic community to demonstrate significant activity against *M. leprosy*, possibly due to its lipophilic properties, which may increase the penetration of the cell wall [37]. The standard dose is 100 mg daily, which gives a peak serum level that exceeds the MIC of minocycline against *M. leprae* by a factor of 10-20. Its bactericidal activity against *M. leprae* is greater than that of clarithromycin but less than that of rifampicin [21]. Minocycline is effective in both tuberculoid [38] and lepromatous cases [36]. Its administration has been associated with lower reactions, particularly in lepromatous cases.

Clarithromycin is a structurally related semi-synthetic antibiotic of the macrolide to erythromycin. Studies of the mouse footpad demonstrated this drug's potent bactericidal activity but it is less effective than rifampicin. The drug is stated to kill 99 percent of *M. leprae* at a dose of 500 mg per day for 58 weeks.

Combination of Newer Anti-Leprosy Drugs

Several combinations of newer drugs between themselves and already established drugs have been suggested and tried over the last few years (Table 1). More than two decades ago, the application of fluoro-

quinolone (FQ) in leprosy treatment is discovered. Past studies were performed regularly based on rifampicin and ofloxacin (RO) for 28 days with rifampicin, ofloxacin, and single-dose moxifloxacin (ROM). The emphasis is on the regular administration of ROM (intermittent treatment) for 12 months in MB and 6 months in PB following the failure of each protocol.

Rifampicin, Ofloxacin, and Minocycline Trial (Single-Dose Therapy)

A multicenter randomized, double-blind, controlled clinical trial by WHO compares ROM efficacy with WHO PB-MDT efficacy in patients with one skin lesion and no peripheral nerve trunk involvement. The study showed that ROM was almost as effective as the WHO standard PB-MDT. No additional observations were reported as ROM for single skin lesion leprosy was withdrawn from the program for operational reasons [39]. In a multicenter, double-blind, controlled single-dose ROM clinical trial in patients with two to three skin lesions, clinical improvement was seen in both regimens [40]. There was no link between the trend of health complications and chemotherapy regimens for long-term follow-up and [41], health incidents were also manageable and relapses and treatment failures in both regimens were not in alarming proportions [39].

Rifampicin, Ofloxacin, and Minocycline Trial (Intermittent Therapy)

The World Health Organization later started further clinical preliminaries with ROM given irregularly in both MB and PB sickness. The regulated portion was allowed once every month with no treatment in the middle. The goal was to see clinical reaction, symptoms, and responses (erythema nodosum leprosum and inversion) which may happen during and after the finish of treatment. Two different investigations have been accounted for utilizing numerous dosages of ROM in lepromatous disease: one in the Philippines and another from Brazil; patients had a mean bacillary index (BI) of 4+ at the passage to the examination, and the fall in BI was like the gathering on WHO MB-MDT [40]. Skin lesions improved as did the histological changes in their skin biopsies during treatment. In the Philippines study, the BI kept on falling after the fruition of treatment, and no backslides were recorded during the ensuing 64 months (> 5 years).

Moxifloxacin-Based Regimens

Findings on clinical research of leprosy using moxifloxacin-based regimens were published for the first time in 2009. Further findings on clinical parameters were published in 2013 and 2019. In recent years, moxifloxacin (FQ) and rifapentine (a long-acting rifamycin derivative) have been reported as having highly promising antimycobacterial activity [42].

Specific new regimes can be graded as absolutely

super visible and as self-administered medications regularly. Some of these studies are clinical trials involving the combination of ofloxacin with dapson (DDS) and CLF [36], and OFLO with rifampicin (RMP) [43], which have been reported to be beneficial in the treatment of lepromatous leprosy. Similarly, a combination of daily ofloxacin with minocycline and monthly rifampicin was also evaluated [44]. Another protocol included the normal MDT-MB with the addition of ofloxacin and minocycline once a month. Ji, et al. have shown that in mice, single doses of the combination of minocycline and Clarithromycin with or without ofloxacin administered once monthly along with monthly doses of 600 mg RMP are completely active against *M. leprae* [45]. The trial, including 600 mg of Rifampicin + 100 mg of Minocycline + 400 mg of Ofloxacin once a month combined with 50 mg of clofazimine and 100 mg of dapson daily for one year, showed that the drugs were well tolerated, that the clinical response to the treatment was very good and that there was no treatment failure [46].

Marie, et al. in their recent systematic meta-analysis reported none of the evaluated regimes showed any benefit over MDT for patients with PB or MB for relapses. The addition of clofazimine to PB MDT did not show significant improvement [47]. Nonetheless, high cost, increased risk of adverse drug reactions, and other technical factors hinder the adoption of such regimens on a large scale. Some studies have also shown that second-line anti-leprosy regimens are either not beneficial or only marginally superior to existing WHO-MDT regimens, even in rifampicin-resistant cases [33,48].

Fixed-Duration Treatment (FDT)

Over time, the duration of leprosy treatments has gradually been shortened: In the early 1990s, the concept FDT was introduced for control programs. It was argued that treatment in PB cases should be stopped after the completion of six supervised doses taken within a maximum of 9 months and that treatment in MB cases should be stopped after the completion of 24 supervised doses within 36 months, irrespective of whether the tests were positive or negative. For cases of MB, this period was further shortened to 12 months, and a single-dose regimen comprising rifampicin (600 mg), ofloxacin (400 mg), and minocycline (100 mg) (ROM) was prescribed for cases of mono-lesion [49,50]. Although FD-MDTs have the advantage of improved compliance and have been successful in other mycobacterial diseases such as tuberculosis, their use is not without limitations, especially in leprosy; for example, the cure or endpoint of treatment for PB cases (smear-negative patients) has been more difficult to define, as opposed to MB cases where slit-skin smear are indicators of disease activity.

Uniform Multidrug Therapy (U-MDT)

To shorten the duration of treatment and simpli-

fy drug supply logistics, a multicenter study has been launched to assess the efficacy of the WHO-recommended 6-month MDT-MB regimen is given to all types of leprosy, both MB and PB. Patients are to be actively followed for a minimum period of 8 years after completion of treatment to monitor reactions and relapses but no conclusions can yet be drawn [51].

A-MDT (Accompanied MDT)

Accompanied MDT (A-MDT) involves providing a full course of treatment to some patients on their first visit to the leprosy clinic following diagnosis. The WHO recommends that A-MDT be user-friendly and appropriate for mobile populations and patients living in remote areas and areas of civil conflict. As an innovative approach to ensuring that such underserved groups have access to MDT and others.

Although MDT remains effective in most cases, there may be relapse (or possibly re-infection). Although relapse rates are generally low (~1 percent), relapse rates in some areas are unacceptably high. Relapse rates are dependent on several operational factors. In general, at the time of diagnosis, higher relapse rates are observed in patients with a high BI, indicating that these patients will likely need longer treatment. When relapse does occur, it is often related to poor MDT compliance. The efficacy of MDT will also disappear with the development of drug resistance. Resistance to dapsons is fairly common and the net effect, along with noncompliance with clofazimine, is that patients receive monotherapy with rifampicin. This situation is considered to be highly conducive to the development of resistance, and several investigators have reported multidrug-resistant of *M. Leprosy* [52,53].

Role of Immunotherapy in the Treatment of Leprosy

Despite the positive impact that WHO-MDT there are many indications that further effort is required to prevent the re-emergence of leprosy and their effort is required to prevent the re-emergence of leprosy and continue efforts toward eradication. That effort should include an effective drug with potential for both prophylactic and therapeutic use. Vaccine hunting as a weapon for primary prevention of leprosy still going on. Besides the presence of a small population of viable

organisms ('persisters') after therapy, there is often a problem with the persistence of a large pool of dead bacilli. Immunomodulators that can stimulate cell-mediated immunity (CMI) have been used to reduce this pool. These agents can be divided into three broad groups: drugs, antigen-related mycobacteria, and other immunomodulators. In the drug category, levamisole and zinc were reported to be useful when used as an adjunct to dapsons therapy, as seen by clinical improvement in lesions and a decrease in the incidence and severity of reactions [54]. Although both are considered immunopotentiators of CMI, their exact mechanisms of action are not fully understood. Also, these compounds have not been adequately investigated in combination with MDT.

Immuno-Therapeutic Effect of MIP

Adding immunotherapy in the form of Mycobacterium w (Presently known as Mycobacterium Indicus Pranii or MIP) vaccine to chemotherapy is intended to accomplish more effective killing of viable bacilli and persistent species as well as faster clearing of dead bacilli and their body components [55]. It is supposed to result in a successful reduction in the length of treatment and enable patients to manage more cases and to increase medication compliance. Numerous drugs and biological tests as immunotherapy and immuno-prophylactic agents in leprosy are focused on cultivable mycobacteria, such as bacillus from the Indian Cancer Research Center (ICRC), Mycobacterium w (Mw), Mycobacterium Habana, bacillus Calmette-Guérin (BCG), *Mycobacterium vaccae*. Of these, Mw (Table 3) and BCG are the most well studied.

Zaheer, et al. (1993) attempted to determine the effect of MDT and Mw in BL/LL whether immunization can accelerate recovery and reduce treatment time by invigorating cell-mediated immunity and observed rapid bacteriological clearance and histological improvement in these patients [56,58]. The immunotherapeutic potential of a single dose of killed ICRC vaccine at the start of therapy with conventional MDT also shows a significant and rapid fall in BI in the vaccinated group as compared to controls [66]. *M. vaccae* has also been suggested as an immunotherapeutic agent, as they also share certain antigens with *M. leprae* [67]. Stanford, et al. used BCG + *M. vaccae* as immunomodulators in contacts and leprosy patients and showed beneficial results [67].

Table 3: Immuno-therapeutic trials with MIP.

Author	Intervention	No. of Cases, & Controls included	Result
Zaheer, et al. (1991) [56] (Case report)	Four doses of <i>M. w</i> administered to lepromatous leprosy (LL) patient	1	After 15 months of treatment, this patient attained bacteriological negativity and clinical inactivity. Histo-pathologically the patient upgraded to borderline-tuberculoid at 12 months, and at 15 months showed features of nonspecific infiltration in the dermis. The rapid immunological upgrading is seen in the patient.

Mukherjee, et al. (1992) [57]	Mw is used in conjunction with a standard chemotherapeutic regimen in MB patients.	122 (vaccine group-87, control group-35)	The histopathological profile of the initial 87 patients in the vaccine group, 35 in the control group) have been observed. The vaccine group received multidrug therapy (MDT) and eight intradermal injections of M. w. every 3 months; the control group had MDT with starch injections as a placebo. The results show a significantly higher proportion of biopsies with histopathological upgrading and/or clearance of dermal granuloma among the vaccinated cases. The number of patients becoming bacteriologically negative was higher in the vaccine group.
Zaheer, et al. (1993) [58]	Combined immunotherapy with Mycobacterium vaccine with a standard multidrug regimen given MB leprosy patients	Total 81 (LL patient vaccine group-17, control-15), BL (14 vaccine, 10 control group), BB (14 Vaccine, 11 control)	Clinical improvement in the group given the vaccine was shown by a more rapid fall in Ramu's clinical score in association with flattening and regression of lesions in contrast to the group receiving multidrug therapy alone. At 12, 18, and 24 months, the fall in clinical scores was statistically significant in BB and LL vaccine group patients but not in control patients ($P < 0.01$). In BL leprosy it was significant at 18 and 24 months ($P < 0.01$).
Kar, et al. (1993) [59]	Mw was given in addition to standard MDT to M B lepromin negative patients belonging to BB, BL, and LL types of leprosy (vaccine group).	106 (53 vaccine group). An equal control group received MDT and injections of placebo)	The incidence of reversal reaction (RR) was marginally higher in the vaccine group (22.6% vaccine group vs. 15% control group).
Sharma, et al. (2000) [60]	Mw in addition to standard MDT, given to bacteriologically positive, lepromin negative MB leprosy patients compared the control group who received a placebo injection in addition to MDT	300 (156 vaccine group, 145 control group who received a placebo injection in addition to MDT	The fall in clinical scores and bacteriological indices was significantly more rapid in vaccinated patients, from 6 months onward until years 2 or 3 of therapy. However, no difference was observed in the fall in bacteriological index in the two groups from year 4 onwards
Sarkar, et al. (2001) [61]	Four doses of Mw given to MB patients along with standard therapy	40 (20 in study group MDT + Mw, 20 control group MDT only)	A patient receiving Mw + MDT shows significant improvements in histopathological, immunological parameters in comparison to the control group receiving only MDT. The incidence of type 1 reaction was more in the Mw + MDT group (30% vs. 10%), while the incidence of type 2 reaction was more in the Control group (25% vs. 15%).
Katoch, et al. (2004) [62]	Mw is given to untreated BL/LL patients with high BI cases, along with standard MDT. One of the three treatment groups was assigned. the control group received distilled water, another group received BCG, and another group received M. w every 6 months	36 BL/LL patient (12 patient in Group I receiving WHO MDT + BCG, Group II patients received MDT and Mw, Group III Control patients received MDT with 0.1 ml of distilled water	Histologically patients in both the immunotherapy groups (groups I and II) showed accelerated granuloma clearance, histological upgrading, and non-specific healing
Narang, et al. (2005) [63]	Standard MDT has given to Untreated MB patients in two comparison groups Mw + MDT, BCG + MDT	60 (20 in Group A M.D.T. + BCG intradermally, 20 in Group B M.D.T. + Mw, 20 in Group C M.D.T. + normal saline as placebo.	BCG exhibited a slightly better and faster effect on bacteriological clearance and clinical improvement as compared to the Mw vaccine in borderline lepromatous (BL)/polar lepromatous (LL) patients with a high initial B.I., however, their effect on histo-pathological (decrease in granuloma formations) improvement was comparable.

Kamal, et al. (2012) [64]	Mw is given to untreated borderline leprosy patients in Non-randomized fashion along with standard MDT	270 (150 cases in one treatment (trial) group (Mw vaccine plus MDT) and 120 cases in another treatment (control) group (MDT only)	Faster clinical recovery from disease and histopathological faster granuloma and bacillary clearance and lesser incidences of reactions were observed in an Mw + MDT group in comparison to MDT only
Kamal, et al. (2017) [65]	Double-blind placebo-controlled study: MIP vaccine added to standard MDT regimen in patients with borderline tuberculoid leprosy	90 (46 patients (13 BT, 11 BB, 22 BL) were in group 1 (intervention, MDT + MIP) and 44 patients (23 BT, 13 BB, eight BL) were in group 2 (control, MDT + placebo)	The preliminary result shows faster bacillary clearance and clinical recovery Early (initial 6 months) occurrence of Type 1 and 2 lepra reactions when compared with the control group due to the immunomodulatory effect of the vaccine. Later (6-12 months and beyond) incidence of reactions was found to be lower indicating reduced morbidity due to reactions in the vaccinated group

In a combined chemotherapy and immunotherapy study conducted by Katoch, et al. (2004). In untreated BL/LL patients with high BI cases, one of the three treatment groups was assigned. All patients received a modified MDT regimen [68] but also, one control group received distilled water, another group received BCG, and another group receives *M. w* every 6 months until *M. leprae* was no longer seen in skin smear. In both groups receiving immunotherapy, no viable bacilli could be detected after 12 months of therapy as assessed by mouse footpad inoculation and ATP estimate of skin biopsies, whereas in control cases viable bacilli could be detected up to 18 months by mouse footpad and 24 months by ATP estimate. While all patients in the MDT plus Mw group became smear-negative for 36 months of therapy, patients in the MDT plus BCG group became smear-negative for 42 months. On the other hand, patients in the control group who were on MDT + distilled water were still smear-positive at the end of 4 years with mean BI of 0.45 and all of them became smear-negative at 5 years. Patients in both immune-chemotherapy groups showed histological improvement and accelerated granuloma clearance [62]. In a related study, untreated MB patients with mild BI were administered MDT for 12 months and one of three therapies (saline, intradermal BCG, or *M. w*, each administered for four cumulative doses at 3-month intervals). Patients in the BCG group reported a slightly higher increase in the clinical score relative to those in the *M.w* at 12 and 24 months. *M. w*, for both BCG and *M. w* groups, showed decreased clinical scores relative to the MDT-only control group [63].

Kamal, et al. (2012) conducted a non-randomized study in which patients with borderline leprosy (BT, BB, BL) were serially recruited into two treatment groups. Group, I (Mw vaccine + MDT) included a total of 150 cases of BT-61, BB-54, BL-35, and 120 cases of BT-51, BB-43, BL-26 of borderline leprosy in group II (MDT only) [64]. Standard MDT according to the type of disease was given to all the patients in both groups. Mw vaccine 0.1 ml was administered intradermally to the treatment group at the start of treatment. BT cases were followed up at 6 doses of normal WHO MDT and 2 doses of MW vac-

cine, BB cases were followed up at 24 doses of MDT and follow-up at 5 doses of MW vaccine. This study shows that the efficacy of adding immunotherapy to normal MDT has resulted in faster clinical recovery from disease, faster histopathology of granuloma and bacillary clearance, and lower reaction incidences.

The immunotherapeutic effect of MIP in patients affected with leprosy was also studied in a randomized double-blinded placebo-controlled trial conducted by Kamal, et al. in 2017 (own study) shows faster bacillary clearance and clinical recovery [65]. Type 1 and 2 leprosy reactions occur early (initial 6 months) as compared with the control group due to immunomodulatory effects of the vaccine. The rate of reactions was found to be lower later (6-12 months and beyond), suggesting a decreased morbidity due to reactions in the vaccinated community.

Conclusion

Current MDT regimens are highly successful in the majority of cases of leprosy but concerns about compliance and possible development of drug resistance, occurrences of relapses, and reactions will continue to be of great concern for eradication from the world. However, the occurrence of new cases of the disease proved that significant transmission is continued. A successful strategy for the eradication of the disease is therefore required to effectively treat the last case that could break the transmission of the disease by offering newer treatment strategies with prolonged defense against infection. Recently newer drug regimens, especially adding FQs or immunotherapy in the form MIP vaccine with standard chemotherapy, have shown excellent efficacy against *M. leprae*, and therefore there is sufficient evidence for incorporating these newer treatment regimens.

As of now, there is no consensus on the use of leprosy vaccines as an immunotherapeutic agent in the National Leprosy Eradication Program in India due to the limited findings of previous studies; however, recent work by many authors shown faster clinical recovery from disease, histopathologically faster granuloma, and

bacillary clearance and lesser incidences of reactions appears to be a very effective and promising method by addition of immunotherapy with chemotherapy and therefore there is sufficient evidence to incorporate this immunotherapeutic treatment strategy into the National Leprosy Eradication Program.

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Conflict of Interest

The authors declare no conflict of interest.

Authors Statements

All the authors have equally contributed in this article.

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