Review Article

Review on Diverse Issues in Improvising Drugs for Treating Leprosy

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ABSTRACT

Leprosy control depends exclusively on case recognition and management with multi-drug therapy. This approach is based on recognizing and treating chronic infectious diseases with effective drug combinations limits the materialization and spread of existing drug resistant pathogens. Besides, tuberculosis educated the relapse cases that are under risk for drug resistance which can destabilize the control measures on hand. Consequently, the construction of multi-drug therapy like approach for controlling leprosy involves systematic evaluation of treatment failures. Several studies have recognized relapses after MDT and drug-resistant strains of *Mycobacterium leprae* have been identified. In this review, we describe the drugs used to treat leprosy and the need for addition of novel drugs in MDT to improve treatment of leprosy patients.

Keywords: Leprosy; Facts; Drugs; Resistance; Multi drug therapy.

INTRODUCTION

Leprosy is an ancient and most dreaded disease, with the fact of its distinctive pathological alterations in a 4,000-year-old human skeleton in India. It was suggested that *Mycobacterium leprae* (*M. leprae*) progressed either in East Africa or South Asia, prior to spreading in Europe and other parts of the World. The most primitive data for leprosy is in Asian texts dated to 600 B.C.[1]. Victims were legally considered as dead, and set apart from the 'living'. Eventually, the leprosy was almost constrained to the 'poverty belt' of the developing world[2], due to the dreadful deformities it created, ambiguity around its aetiology, spread and need of any efficient therapy till recently[3].

Certainly, it has been a long way from the era with inadequate information bordering on ignorance about the disease, on extent of the problem, extreme negative image which led to prevention by isolation of patients and need of organised services[4]. However, the detection of *M. leprae* by Armauer Hansen and the treatment of leprosy with chaulmoogra oil generated hope that leprosy is treatable. In 1941, the emergence of dapsone and later, in 1981, the execution of multi drug treatment (MDT) distorted the complete scenario[5]. MDT has been the key weapon against leprosy and by 2005, the prevalence in India was less than 1/10000. This was a milestone in the history of leprosy in India[6]. Leprosy elimination campaigns were in progress in endemic countries. The outcome of the campaigns was the 'cure' of more than 10 million patients, within 2000. During the last two decades, the global prevalence of leprosy has dropped by nearly 90 per cent, by the joint efforts of the World Health Organization (WHO), local governments, health professionals, and non-governmental organizations[7].

In reality, there is a necessity to prolong and afford worth leprosy services to all through general health services. All these services in the integrated health care approach will go further in dropping the stigma. Efforts are required to lessen deformity in the course of early detection, physiotherapy, reconstructive surgery, self care and developing sound surveillance systems. With all the significant attainments in the struggle against leprosy, the phase is now put for the ultimate assault. There is requisite for research on tools for early diagnosis, effective treatment, shorter duration and prevention of malformations. Assessing the role of immunotherapy, immunoprophylaxis and the discovery of novel drugs may proceed to better understand their mode of action. Further, the molecular analysis of *M. leprae* genome may endow with the requisite basis for all this. It is anticipated that with the efforts of all ventures and strong political force, the leprosy will be stamped out in the near future[3].

Specifics on Leprosy

About 55% of leprosy cases in the world are in India, where, about 1, 27,000 new cases were reported between 2010 and 11[8]. About 12,463 leprosy new cases between 2010 and 11 were children and more than 10% new cases detected in nine states were children. In particular, the leprosy is widespread among the poorest and most marginalized communities, owing to their need of access to healthcare, deprived sanitation and overcrowded living spaces. Between 2010 and 11, about 14.31% of new cases were with scheduled tribes and 18.69% with scheduled castes, though these groups figured for only 8.2% and 16.2% of the population, respectively in 2001. In some locale, leprosy is a rising setback. In India, about 14 states detected increased leprosy new cases in 2010-11 compared to 2009-10. Several districts persist to have prevalence of leprosy greater than the WHO benchmark for eradication of

leprosy, while India on record 'eliminated' leprosy in 2005. Some leprosy patients endure deformities, which can end with lifelong disabilities and need an extensive and sustained care[9].

In specific, the leprosy cases are not evenly distributed; however tend to cluster in some localities, villages or taluks. Thus, even the country as a whole has eliminated leprosy; Bihar and Chattisgharh are yet to achieve elimination. New leprosy cases persist to occur in almost all endemic countries and high-burden exist next to a low-burden background. As reported by 105 countries, the new leprosy cases detected during 2011 was 219,075 and India hit highest in the list with its input of 58.1% to the pool. Intensified and focused measures with MDT have condensed the leprosy burden, however, supporting the same intensity of focus and loyalty will be a challenge, particularly in low-resource background, where equity of admittance is an issue[10].

There are huge divergence in developments and in year-to-year trends among regions and countries. In spite of the apparent global decline, an increase in new cases was detected over the past 2 years in China, Indonesia and Mozambique. Besides, the prevalence ratio to case detection range from 0.6 in India and 0.7 in Brazil, to greater than 5 in Morocco, Cape Verde and Hong Kong. Moreover, the range in female proportions is highest in Africa and least in Western Pacific. This may reflect relative access of females to services in some countries, moreover, this will reflect actual variations in leprosy ecology and age of the cases i.e., magnitude of multibacillary and thus, males characteristically increase with age[11]. The high proportion of male leprosy patients is a widespread surveillance. Industrialization, urbanization, and further chances for contact with open cases may possibly comprise some pressure on the sex prevalence. Social customs and taboos, possibly will account for the fewer number of female patients reporting to a hospital. A mass of the cases was from the low income group. Even though lifting the economic standard of the common population is not a definite antileprosy measure, it is distinguished that leprosy control has constantly been coupled with a rise in its socioeconomic standard in every country. Several cases were between 20-29 years of age, signifying that adults are more commonly affected than children. These statistical divergences are attributable greatly to operational differences among programmes, which make evaluation unfeasible, in the lack of complete information on strategies of various countries[12].

Drugs in Treating of Leprosy

Chaulmoogra oil and the instigation of leprosy control

Previous to the era of antibiotics, the chaulmoogra oil, an extraction from the seeds of *Hydnocarpus wightiana*, was used to treat leprosy, with some degree of success[13]. The use of chaulmoogra oil for leprosy treatment in India can be tracked to 600 BC in Sushruta Samhita[14]. The treatment of leprosy with sodium hydnocarpate stroked the launch of leprosy control in India. In late 1915, therapeutic trials were initiated with sodium chaulmoograte and launched in India during British Empire. The chaulmoogra syringe attained an iconic status in the hospitals. During the nineteenth century, the view of British colonial physicians in utilizing the chaulmoogra and marotti oils was at discrepancy. Although the oils sustained to be employed, it was by default to a certain extent than proven worth and patient fulfillment. However, the patients often refused to persist with oral treatment, due of nausea and gastric irritation. Injections also did not get much support with the patients as multiple painful needle punctures were given twice-weekly to deliver 5 ml of drug. However, the Hydnocarpous and chaulmoogra oils preserved their place in the British Pharmacopoeia till the 1940s[15].

In the modern age of leprosy treatment during 1940s, promin showed significant benefits in treating the leprosy. This discovery hit the inceptions of real hope for the successful treatment and cure of leprosy[16]. Further effort to limit the toxicity of treatment led to the start of dapsone, the parent compound of promin, which was extensively used as long-term monotherapy until 1970s[17]. The preface of dapsone simplified the treatment and altered the face of leprosy noticeably[15].

Dapsone and the emergence of resistance

In the 1970s, the initial zest of finding a therapy for leprosy was dampened by relapses and emergence of drug resistance to dapsone[18]. The first information of primary dapsone resistance was acknowledged in 1977[19]. Followed by the footpad-proven secondary resistance, was a growing number of countries worldwide with 2-3 % of range in frequency[20]. With the realization of wide reaching increase in dapsone resistance in *M. leprae*, dapsone monotherapy was no longer considered sufficient for treating leprosy[21,22]. Thus, there was an urgent need for safe and combined drug regimens effective in treating leprosy and preventing drug resistance[23].

In response, WHO maintained the establishment of the special programme for research and training in tropical diseases in 1976 to assess valuable responses to dapsone resistance and to encourage the development of vaccines[16]. In the 1960s and 1970s, various antitubercular drugs such as streptomycin, ethionamide, prothionamide, isoniazide, and thiacetazone were attempted as second-line drugs; however, their inconsistent efficacy, systemic toxicity, cross-resistance and cost demonstrated to be limiting factors[24]. The perception of MDT in leprosy cropped up after the availability of clofazimine and rifampicin since the familiarity in the therapy of tuberculosis[25-28]. Based on the theoretical considerations, leprologists worldwide initiated the combined drug regimens for treating leprosy on an experimental basis.

As *M. leprae* cannot be cultivated *in vitro*, the frequency of drug-resistant mutants has been inferred from studies with *M. tuberculosis* or other cultivable mycobacteria. Consequently, the frequency of dapsone, rifampicin and ofloxacin resistance appears to be high than the clofazimine resistance in *M. leprae* which remains unknown but appear to be extremely low[29].

Multi Drug Therapy

In 1981, WHO set an immense decision and recommended MDT for leprosy. MDT is also not an ideal tool and it has its inadequacy like long duration of treatment, poor compliance, irregular treatment, minor and sometime serious side effects, rifampicin/multidrug resistance, high relapse rate 0.65 to 3.0 per cent for PB and 4 to 7 per cent for MB[30]. Only dapsone, rifampicin and clofazimine have been used to any considerable extent to treat leprosy patients and are components of the multi-drug regimens favored by the WHO to treat leprosy[31].

In the past 2 decades antimicrobials of three groups, fluoroquinolones, macrolides and tetracyclines have been found bactericidal for *M. leprae* in mice and more rapidly clear viable bacilli from patients than dapsone and clofazimine, suggesting these may prove superior components of future MDT regimens. In fact, for certain leprosy patients, those with single lesion PB leprosy, the WHO have already recommended treatment with a single dose of rifampicin, ofloxacin and minocycline. All these can have severe implications, in view of the huge number of leprosy cases in India. Relapse and resistance to MDT entitled the development of new/ alternative MDT regimen, which is of short duration, more effective, free of side-effects and preferably, free from the fear of emergence of drug resistance[32].

Materialization of new drugs

WHO Steering Committee on chemotherapy of mycobacterial diseases suggested that the exploration for novel drugs and new drug regimens must persist to consolidate labors towards the target of eradication of leprosy, enhanced patient fulfillment, to extend alternate agents against dapsone /rifampicin/clofazimine resistant bacilli and to develop organized regimens for anticipation of drug resistance[18]. Some new drugs exist to replace those being presently used in MDT. These drug combinations are planned, with the rationale of reducing relapses or for drug resistance. In recent years, a number of new antimicrobial agents show exceptional anti-leprosy activity both in clinical trials and in animal studies. It is essential to consider that newer drugs must have an exquisite bactericidal activity, have no opposition with existing drugs, an oral route of administration and cost-effective. Of the several new drugs, ofloxacin, moxifloxacin, minocycline and clarithromycin displayed a high bactericidal activity against *M. leprae* in animal and human trials. To date, however, there is no consent as to which combination of drugs would be most suitable[24].

Trials are being performed to develop antileprosy regimens of short duration that are extremely effectual and have low occurence of toxicity and side-effects. Several drug combinations that have exposed promise are rifampicin, ofloxacin and minocycline (ROM); clarithromycin, minocycline and ofloxacin; rifapentine, moxifloxacin and minocycline (PMM) and inclusion of these new drugs to the WHO MDT like MDT supplemented by ofloxacin, or ofloxacin plus rifampicin[33-37]. The absolute outcome of these studies along with rate of relapse, subsequent to long-term follow up upto 10 years will be supportive in fix on alternative and improved regimens for leprosy[38].

Perhaps, the requirement is a single MDT regime of a duration that is acceptable for all categories of leprosy[39-41]. This will make error of sorting in the field irrelevant and lessen the operational and logistic complexities of sustaining satisfactory supply of drugs. Though the expenditure of therapy per month will rise, the cost on the whole to the programme will most likely not change much, as the duration of therapy will be less and the number of patients currently being detected annually is also lesser than before. There are concerns as regards the overtreatment of paucibacillary patients. However, a uniformly efficient regimen as that of tuberculosis will do away with the potential drawback of false categorization and under treatment, and a degree of overtreatment appears suitable in efforts to further hasten the development and consolidation of leprosy eradication[38].

Implementation of Combined Drug Regimens

Prednisolone, Azathioprine, Thalidomide

Prednisolone is used for its anti-inflammatory activity in moderate, severe and recurrent erythema nodosum leprosum (ENL), having an early therapeutic action and being easily obtainable. The chronic and recurrent ENL patients on steroids are at larger threat of becoming steroid dependent. The huge immune-suppressive doses of steroids for extended periods frequently result in side effects. At present, the intravenous methylprednisolone is customary in treating various disorders[42].

Azathioprine is used, formerly, in several dermatological conditions[43,44]. It is a purine antagonist derived from 6-mercaptopurine with an imidazole ring. It mostly affects rapidly dividing cells, particularly of the bone narrow. Accordingly, the principal side-effects are bone narrow depression, oral ulcerations and gastrointestinal upsets. On its long-term use, the other side effects viz., cutaneous infections, haematopoietic tumours and neoplasia are seen. It is found to be successful along with prednisolone, both as a steroid sparing agent and immunosuppressive, for the treatment of reverse action[45].

Thalidomide was introduced as treatment for ENL. Thalidomide's antipyretic action was greatly effective in reducing symptoms of ENL. Its ability in controlling neuritis, the main cause of eternal disabilities in leprosy,

was restricted. However, prednisolone is much effectual in controlling ENL and associated neuritis[46].

Clofazimine

Clofazimine, an anti-leprosy drug was introduced during 1960, for its anti-inflammatory action[47]. It is the drug of choice for the management of chronic and recurrent ENL reactions. Moreover, it was found that none of the patients given clofazimine for ENL reactions relapsed, though almost all patients treated with thalidomide relapsed after discontinuation of the drug[48]. The clofazimine is currently a chief component of the multidrug therapy (MDT) which is introduced as the standard treatment for leprosy, as given by WHO in 1981. The existence of clofazimine in the combination has extensively reduced the frequency and severity of ENL reactions worldwide[49].

Glucocorticosteroids

Glucocorticosteroids (GCS) are the major therapeutic agent used in the treatment of leprosy reactions[50]. Corticosteroid-sparing agents are used specifically to reduce the GCS doses necessary to manage the disease and to lessen side effects, in patients with rheumatological diseases[51]. After methotrexate, azathioprine is the most widely used immunosuppressant due of its immunosuppressive effect, superior to methotrexate, with less serious side effects than cyclosporine, and a lesser cost than that of mycophenolate, tracolimus and sirolimus[52].

Disubstituted thiourea compounds

Thiambutosine is the best recognized of the disubstituted thiourea compounds. Its effects are virtually toxic free, but bacterial resistance develops possible after about two years. Thiocarlide and dialide are the alternative compounds for oral use, which appear to be effective. Thiacetazone is another recognized antileprosy drug, however, has been largely displaced by the non-toxic thiambutosine[53,54].

Gastric effects may occur which can be overcome by taking the tablets with food. Other side effects are unusual and include vertigo, headache, proteinuria, anaemia, skin eruption, hepatitis and agranulocytosis. Most likely, leprosy bacilli that are resistant to thiacetazone will be cross-resistant to thiambutosine, which has been observed in experimental tuberculosis and in mouse footpad infections. This riminophenazine dye holds an exceptional point in leprosy treatment as it combines an antibacterial action, similar to that of dapsone, with an anti-inflammatory action of proved value in restraining the materialization of lepra reaction[55].

Pefloxacin, Ofloxacin, Minocycline, Rifampicin

Pefloxacin emerged into a better drug with overall clinical response than did ofloxacin. It was found that pefloxacin was superior to ofloxacin in killing *M. leprae* within 14 days, while the reverse was true at later time intervals[56].

The single doses of ROM therapy for single lesion paucibacillary leprosy was assured and recommended by WHO, however, the exact place of fluoroquinolones in the therapy of leprosy left undetermined[57]. WHO MDT includes only dapsone, clofazimine and rifampicin; and the role for fluoroquinolones in treating leprosy to date has been restricted. It was found that rifampicin combined with sparfloxacin resulted in better antimicrobial activity and the combination of sparfloxacin, rifampicin and minocycline is more potent than the combination of rifampicin and minocycline. Besides, the minocycline combined with rifampicin and ofloxacin with rifampicin confirmed convincingly superior to rifampicin alone. In this hold, moxifloxacin and rifapentine, which in mice were confirmed superior to ofloxacin and rifampicin, respectively, might establish predominantly efficacious components of a newer generation MDT for MB leprosy. Rifampicin was more effective, but its use in leprosy is strictly limited by its prohibitive cost[58,59].

Some antibiotics were found successful, such as cycloserine and terramycin, however, the most effective appears to be rifampicin. It is twice as effective as dapsone in treating infected mice. Corticosteroids showed dual anti-inflammatory and immunosuppressive actions and regarded as the drugs of choice in the treatment of reactions and neuritis in leprosy. They act in dropping the cutaneous and intraneural oedema, leading to a quick development and reduce in post-inflammatory scar formation, all through the prolonged healing phase. Their main effect is to suppress the T-cell driven inflammatory response to *M. leprae* within nerves and skin. Almost half of the patients with or develop reaction throughout the course of the disease acquire steroids[60]. Ofloxacin and minocycline were more bactericidal than dapsone and clofazimine in both mice and clinical trials. The skin pigmentation caused by clofazimine is difficult. It accumulates in leprosy lesions and subsequently exposes lesions on the face thereby causing a generalised tanning of the skin and an icthyosis on the legs[61].

ROM was found much expensive than MDT, however, a single monthly dose might not be prohibitively expensive. The potential advantages exhibit that it might be easier to execute monthly supervision with this treatment in order to improve detection of reactions and nerve damage. The patients were found more likely to meet the terms with the medication, although they do not attend clinic, as the drugs showed fewer side effects. The replacement of rifapentine instead of rifampicin and moxifloxacin instead of ofloxacin must also be measured[62,63]. These two drugs showed bactericidal effect against *M. leprae* in mouse models. Besides, moxifloxacin was found significantly bactericidal in patients with lepromatous leprosy, and hence, may possibly be considered as an alternative for enclosure in a monthly regimen[64,65].

DISCUSSION

Basic research in the immunology of leprosy reactions remains crucial for the understanding and the development of more powerful drugs for their control and prevention. Moreover, the relapse cases are at threat for drug resistance and can undermine prevailing control measures and there has been a burst of activity towards the development of efficient drugs, because of the increasing resistance of *M. leprae*.

Hence, developing studies using inclusion of novel drugs in MDT is a potentially exciting way to improve leprosy treatment for patients and to help in the next stage of leprosy control.

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