IJBPAS, September, 2021, 10(9): 3141-3149

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

UPDATES INLEPROSY TREATMENT

BALAKRISHNAN L[1], EDWARD V[2] AND EDWARD S[3*]

1: Final Year MBBS Student, Sree Balaji Medical College and Hospital, Chennai

2: Assistant Professor, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai

3: Professor, Department of Community Medicine, Sree Balaji Medical College and Hospital, Chennai

***Corresponding Author: Dr. Vijaykumar Edward: E Mail: vijayedward973@gmail.com**

Received 26th Nov. 2020; Revised 27th Dec. 2020; Accepted 12th Jan. 2021; Available online 1st Sept. 2021

https://doi.org/10.31032/IJBPAS/2021/10.9.5630

ABSTRACT

Leprosy is a chronic, treatable, disease caused by *Mycobacterium leprae*. Modern leprosy therapy typically consists of combinations of dapsone and rifampin with or without clofazimine depending on paubacillary or multibacillary status. The vaccine most commonly associated with leprosy prophylaxis is the BCG vaccine. The newly emerging *Mycobacterium indicuspranii* vaccine is also gaining prominence as a potential method of prevention however its efficacy is lesser than that of BCG. Effort is being made to develop a vaccine specific for leprosy using bio informatic tools to identify genes from *M. leprae*. Additionally vitamin D supplementation has also proven to be a possible treatment pathway for leprosy. Prognostic and early diagnostic tools to accompany therapeutic strategies are also under development. It has been proved that ML0405 and ML2331 are antigens of *Mycobacterium leprae* with potential although its use in a clinical setting is doubtful. In spite of all this the current most effective tool against leprosy is contact tracing and post exposure prophylaxis. Bed aquiline is found more effective against mycobacteria and could be considered for this article.

Keywords: Leprosy, *Mycobacterium leprae,* dapsone and rifampin

INTRODUCTION

Leprosy is a chronic, treatable, disease caused by *Mycobacterium leprae*. *M. leprae* is an acid fact, rod shaped bacillus which primarily affects the skin, peripheral nerves, upper respiratory tract and eyes **[1]**. The disease has severe physical, social, and psychological consequences. Currently leprosy is curable.

WHO has classified Leprosy according to host immunity and bacilli load as follows for treatment purposes:

• **Paubacillary (PB):** a case of leprosy with 1 to 5 skin lesions, without demonstrated presence of bacilli in a skin smear

• **Multibacillary (MB):** a case of leprosy with more than 5 skin lesions; or with nerve involvement; or with the demonstrated presence of bacilli in a slit skin smear, irrespective of number of lesions

At one end of the spectrum are those with high levels of immunity who present with a single, well- demarcated skin lesion with central hypo-pigmentation and hypoesthesia. While those with low levels of immunity feature numerous, poorly demarcated, raised or nodular lesions on all parts of the body. MB leprosy is also associated with neuritis. There is thickening of peripheral nerves with weakness or loss of sensation in the muscles supplied by the nerve **[2]**. Though there has been a sharp fall in the prevalence of the disease worldwide since the 1980s, new cases still continue to arise. As of 2019 the global prevalence was 171 175 **[3]**. In India the prevalence has reduced from 57.8/10,000 in 1983 to 0.57/10,000 in 2019. This decline is attributed to the implementation of Multi Drug Therapy (MDT). Regardless India does continue to account for 57% of new cases reported globally each year and is among the 3 “global priority countries” that contribute 96% of world numbers of leprosy **[4]**.

CURRENT METHODS OF TREATMENT AND DIAGNOSIS

After initial over reliance on dapsone mono therapy, drug resistant leprosy bacilli have developed. Therefore modern leprosy therapy typically consists of MD Tregimens put forward by the WHO Expert Committee (Chemotherapy of leprosy for control programmes: report of a WHO study group WHO 1981). For patients of PB leprosy rifampicin 600mg should be taken once a month along with dapsone 100mg daily for 6 months. Conversely MB patients are prescribed rifampicin 600 mg and clofazimine 300 mgto be taken once a month, dapsone 100mg daily, and clofazimine 50mg for 12 months. This new regimen both combats dapsone resistant strains as well as

shortens the duration of therapy while being generally well tolerated **[5]**.

Rifampicin shows very few toxic effects at the current dosage however it may turn urine slightly reddish which the patient should be notified of before the initiation of therapy. Similarly clofazimine causes brownish black discolouration of skin which gradually disappears on completion of therapy. This too should be explained to the patient. Second line drugs include moxifloxacin, ofloxacin, minocycline, and clarithromycin

In India the National Leprosy Eradication Programme aims to achieve regular treatment of patients by providing MDT at health care facilities. Classic methods of Leprosy diagnosis are based on clinical examination, bacillary counts in skin smear microscopy, histopathology and more recently PCR. These methods cannot distinguishing latent infection from active disease **[7]**.

VACCINES

As discussed above, the current strategy for the treatment of leprosy is based on the implementation of effective multi drug regimens recommended by the WHO. Unfortunately, recently collected data has revealed that this strategy appears to have had little effect on reducing occurrence of new cases of leprosy worldwide. Relapse rates are as high as 16 to 39% in multibacillary patients **[8]**. The use and development of vaccines has therefore been given high importance.

The vaccine most commonly associated with leprosy prophylaxis is the BCG vaccine. So far5 studies have found that the vaccine does provide some protection. However the definitive use of the BCG vaccine as a preventative measure for leprosy remains debatable as there was substantial heterogeneity between the trials. The extent of protection varies from 20 to 80% across the various trials. This disparity can be attributed to the duration of follow up, number of doses, and the year in which the study was conducted. Additionally the trials have shown that the vaccine is more effective in those to which it has been administered before the age of 15 than in those vaccinated later on **[9]**.

Methods to improve BCG usefulness against leprosy are being investigated. A Brazilian study suggests that neonatal BCG vaccination may have an important impact on transmission of leprosy **[10]**.

Other potential vaccine candidates include BCG and heat killed *M. leprae*, BCG and M Vaccae, ICRC bacillus, and *Mycobacterium indicuspranii*. The hypothesis that BCG with killed *M. leprae* improves vaccine efficacy was evaluated by three different studies

which found that no advantage was observed by including heat killed *M. leprae* along with BCG. Of the three remaining candidates *Mycobacterium indicuspranii* (MIP) has been put forward to be implemented as part of the National Leprosy Eradication Programme by the National Jalma Institute of Leprosy.

Mycobacterium indicuspranii elicits a similar antigenic response to the BCG vaccine and its potential in leprosy prevention is being studied. It has shown some success in animal models of tuberculosis. Producing high levels of pro inflammatory cytokines and multifunctional T cells **[11]**. Despite the fact that the MIB vaccine is less effective than BCG in the prevention of leprosy it is also more effective than other existingnon BCG vaccine candidates over a three year period. It's potency does however begin to fall after 6-9 years, indicating a potential need for booster doses if it is considered to be implemented as a leprosy vaccine **[12]**.

Effort is being made to develop a vaccine specific for leprosy however there is difficulty in obtaining a highly reliable source for leprosy antigens. Infected armadillo tissue has been used in the past as a source however purified proteins have been available in very limited quantities and of poor quality, making them difficult to use for vaccine development **[13]**.

Bioinformatic tools are now being used to identify genes from *M. leprae* genome sequence. These tools can identify specialised proteins which share amino acid sequences with M. tuberculosis and also pin point their cellular location and possible secretion across the cell membrane. Finally, the proteins of interest are selected for further study and are purified as recombinant proteins for an endless supply of the protein for immunologic and vaccine studies **[14]**.

Due to the above mentioned difficulties and technological advancements, current attempts at developing a specific leprosy vaccine utilises BCG altered through genetic engineering **[15]**.

VITAMIN D

Vitamin D has been found to be involved in the T cell mediated immune response. When an immature T cell is presented with a pathogen it expresses a receptor for vitamin D. Once the receptor binds with the vitamin it becomes internalised into the nucleus where it then triggers the maturation of the T cell. The micro RNA isolated from skin lesion of leprosy expresses hsa-mir-21 which blocks the T cell gene responsible for maturation **[16]**.

Research conducted in Kolkata, India concludes that a majority of patients suffering from leprosy have lower levels of

vitamin D3. Furthermore those patients suffering from complications such as neuritis had vitamin D receptor expression levels as low as only 5% to 10% that of normal individuals **[19]**. The occurrence of bone deformities in patients of leprosy further supports this fact **[17]**.

Therefore the knockdown of hsa-mir-21 in *M. leprae* infected T cells restored antimicrobial activity against *M. leprae*. As such administering anti-hsa mir-21 to help counter the over expression of hsa-mir-21 induced by *M. leprae*, together with vitamin D supplementation is a possible treatment pathway for leprosy **[18]**.

BEDAQUILINE

Among the newer drugs under trial for use in leprosy, the most promising is Bedaquiline **[19]**.

ANTIBODY RESPONSE IN MONITORING TREATMENT, AND RECURRENCE

Prognostic and early diagnostic tools to accompany therapeutic strategies are also under development. Diagnostic techniques currently being used are based on the appearance of clinical symptoms or of immunoglobulin M antibodies that recognise the bacterial phenolic glycolipid I, are unable to reliably identify early-stage leprosy **[20]**.

ML0405 and ML2331 are antigens of Mycobacterium leprae, they can indicate the presence of infection, however they are not as of yet eligible for use in the clinical setting **[21]**. The serum samples of leprosy patients from Venezuela and Brazil were tested for reactivity against the specific recombinant proteins, ML0405 and ML2331, and the LID-1 fusion protein that incorporates both of these antigens. Antigen-specific IgG was highest in lepromatous leprosy patients and decreased among the other types of the disease, such that only a small proportion of true tuberculoid patients tested positive. Thereby indicating that the levels of antibody reduced with decreasing severity of the disease. The effect of multi drug therapy in the level of antibody was also investigated. Years after treatment, the majority of Venezuelan patients did not possess circulating anti-LID-1, anti-ML0405, and anti-ML2331 IgG, and those that did exhibit seropositivity could be attributed to irregular treatment. At discharge, the magnitude and proportion of positive responses of Brazilian patients against the proteins and phenolic glycolipid (PGL)-I were lower for most of the clinical forms. Therefore with further research these antibody responses could be used as a method of assessing the efficacy of treatment and progression of disease, however as of now their practical use is debatable **[22]**.

CONTACT TRACING

In the absence of definitive methods of prevention the onus falls on rapid identification of potential cases followed by effective chemotherapy. Contact tracing is imperative in this objective. However the consent of the index case is required to notify their contacts of the diagnosis and therefore proceed with contact tracing and post exposure prophylaxis.

Any person who has had contact with the index case for at least 20 hours per week, for at least 3 months in the past year is considered a contact. Those most likely at risk are other household members, neighbours, and social contacts. After being identified the contact must then go through a screening procedure for signs of the disease and any potential contraindications for post exposure prophylaxis.

Important findings in the screening process are signs of leprosy such as hypo-pigmentation and loss of sensation, signs of tuberculosis such as cough, pregnancy, liver disease, and kidney disease.

POST EXPOSURE PROPHYLAXIS

Post exposure prophylaxis (PEP) is given to healthy contacts to reduce their risk of developing to disease. It consists of a single dose of rifampicin. To be eligible for PEP the person should be a confirmed contact, more than 2 years of age, and their consent must be given. It is contraindicated in those who show signs of infection with leprosy or tuberculosis, have a history of liver or kidney disease, pregnant woman, and those who have taken rifampicin therapy within the last 2 years. The recommended dose for adults is 600mg. All patients should be notified of the potential side effects.

CONCLUSION

In conclusion the current leprosy treatment methods, although effective are unable to control the disease to a suitable degree with the rise of obstacles such as multi drug resistance. There continues to be a large amount of new cases diagnosed each year, especially in developing countries such as India. Therefore further research and implementation of other forms of therapy such as those mentioned above along with strict compliance to contact tracing and post exposure prophylaxis will be beneficial in the fight to end leprosy.

REFERENCE

[1] Rao PN, Suneetha S. Current situation of leprosy in India and its future implications. Indian dermatology online journal. 2018; 9(2): 83.

[2] Legendre DP, Muzny CA, Swiatlo E. Hansen's disease (leprosy): current

and future pharmacotherapy and treatment of disease-related immunologic reactions. Pharmaco-therapy: The Journal of Human Pharmacology and Drug Therapy. 2012; 32(1):27-37.

[3] Tripathi KD. Essentials of medical pharmacology. JP Medical Ltd; 2013; 30.

[4] Martinez AN, Talhari C, Moraes MO, Talhari S. PCR-based techniques for leprosy diagnosis: from the laboratory to the clinic. PLoSNegl Trop Dis. 2014; 8(4): e2655.

[5] Gelber RH, Balagon MV, Cellona RV. The Relapse Rate in MB Leprosy Patients Treated with 2-Years of WHO-MDT is Not Low1. International Journal of Leprosy and Other Mycobacterial Diseases. 2004; 72(4): 493.

[6] Convit J, Sampson C, Zuniga M, Plata J, Silva J, Molina J, Pinardi ME, Salgado A, Smith PG, Bloom BR. Immunoprophylactic trial with combined Mycobacterium leprae/ BCG vaccine against leprosy: preliminary results. The Lancet. 1992; 339(8791): 446-50.

[7] Cunha SS, Rodrigues LC, Pedrosa V, Dourado IM, Barreto ML, Pereira SM. Neonatal BCG protection against leprosy: a study in Manaus, Brazilian Amazon. Leprosy review. 2004; 75(4): 357-66.

[8] Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL. The continuing challenges of leprosy. Clinical microbiology reviews. 2006; 19(2): 338-81.

[9] Ngamying M, Sawanpanyalert P, Butraporn R, Nikasri J, Cho SN, Levy L, Brennan PJ. Effect of vaccination with refined components of the organism on infection of mice with *Mycobacterium leprae*. Infection and immunity. 2003; 71(3): 1596-8.

[10] Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL. The continuing challenges of leprosy. Clinical microbiology reviews. 2006; 19(2): 338-81.

[11] Saka HA, Valdivia R. Emerging roles for lipid droplets in immunity and host-pathogen interactions. Annual review of cell and developmental biology. 2012; 28: 411-37.

[12] Mattos KA, Oliveira VC, Berrêdo-Pinho M, Amaral JJ,

Antunes LC, Melo RC, Acosta CC, Moura DF, Olmo R, Han J, Rosa PS. *Mycobacterium leprae* intracellular survival relies on cholesterol accumulation in infected macrophages: a potential target for new drugs for leprosy treatment. Cellular microbiology. 2014; 16(6): 797-815.

[13] Degang Y, Akama T, Hara T, Tanigawa K, Ishido Y, Gidoh M, Makino M, Ishii N, Suzuki K. Clofazimine modulates the expression of lipid metabolism proteins in Mycobacterium leprae-infected macrophages. PLoSNegl Trop Dis. 2012; 6(12): e1936.

[14] Mattos KA, Lara FA, Oliveira VG, Rodrigues LS, D'Avila H, Melo RC, Manso PP, Sarno EN, Bozza PT, Pessolani MC. Modulation of lipid droplets by *Mycobacterium leprae* in Schwann cells: a putative mechanism for host lipid acquisition and bacterial survival in phagosomes. Cellular microbiology. 2011; 13(2): 259-73.

[15] Worobec, S. Current approaches and future directions in the treatment of leprosy. Research and Reports in Tropical Medicine. 2012; 79.

[16] Mandal D, Reja AH, Biswas N, Bhattacharyya P, Patra PK, Bhattacharya B. Vitamin D receptor expression levels determine the severity and complexity of disease progression among leprosy reaction patients. New microbes and new infections. 2015; 6: 35-9.

[17] Kv L, Nguyen LT. Role of the vitamin D in leprosy. The American journal of the medical sciences. 2012 Jun 1; 343(6): 471-82.

[18] Liu PT, Wheelwright M, Teles R, Komisopoulou E, Edfeldt K, Ferguson B, Mehta MD, Vazirnia A, Rea TH, Sarno EN, Graeber TG. MicroRNA-21 targets the vitamin D–dependent antimicrobial pathway in leprosy. Nature medicine. 2012; 18(2): 267-73.

[19] Hartkoorn RC, Uplekar S, Cole ST. Cross-resistance between clofazimine and bedaquiline through upregulation of MmpL5 in *Mycobacterium tuberculosis*. Antimicrobial agents and chemotherapy. 2014; 58(5): 2979-81.

[20] Duthie MS, Goto W, Ireton GC, Reece ST, Cardoso LP, Martelli

CM, Stefani MM, Nakatani M, de Jesus RC, Netto EM, Balagon MV. Use of protein antigens for early serological diagnosis of leprosy. Clinical and Vaccine Immunology. 2007; 14(11): 1400-8.

[21] Reece ST, Ireton G, Mohamath R, Guderian J, Goto W, Gelber R, Groathouse N, Spencer J, Brennan P, Reed SG. ML0405 and ML2331 are antigens of Mycobacterium leprae with potential for diagnosis of leprosy. Clinical and vaccine immunology. 2006; 13(3): 333-40.

[22] Duthie MS, Hay MN, Rada EM, Convit J, Ito L, Oyafuso LK, Manini MI, Goulart IM, Lobato J, Goulart LR, Carter D. Specific IgG antibody responses may be used to monitor leprosy treatment efficacy and as recurrence prognostic markers. European Journal of clinical microbiology& infectious diseases. 2011; 30(10): 1257-65.