CONTINUING MEDICAL EDUCATION

VACCINES IN LEPROSY

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The last 2 decades have seen a rapid decline in leprosy case load through out the world, the total number of patients having come down to around 1.2 million as against over 13 million in 1980.[1] This decline in numbers has been due to wide application of MDT. Not only has the prevalence rate come down, the profile of patients has also shown a shift towards early disease,[2] and fewer deformities among newly detected patients are being observed.

However, new leprosy patients continue to be detected in almost all areas. The decline in new case detection rate (NCDR) has been marginal, if any and about 0.5 to 0.6 million new cases are diagnosed each year,[3] despite the fact that a majority of registered patients are being given MDT. This is on account of there being large numbers of hidden cases,[4] and hence the continuing pool of infection in the community. Susceptible individuals are, therefore, prone to get infected and develop disease. The present strategy of intensive case detection and bringing all the patients diagnosed under treatment is likely to further reduce the number of active cases and hence the pool of infection. However, the eradication of the disease may not be achievable unless some measures are adopted to boost the immunity of the community, so that even if infection does not take place, disease is not allowed to develop because of competent immune response as happened in small pox. In fact immunoprophylaxis has been considered the most cost effective way for eradication of infectious diseases.

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Vaccine testing and/or development, relevant to leprosy has involved a) measuring immune conversion in persistently lepromin/ M.leprae soluble protein antigen (MLSA)/SPA) negative leprosy patients (both indeterminate and lepromatous), b) studying T cell function in lepromatous patients and the effect of reagents in improving lymphocyte/macrophage functions, c) mouse studies showing inhibition of M.leprae multiplication, d) immunotherapeutic potential, e) specific immune conversion in healthy contacts and f) measuring protection in total population which involves follow up and comparison of incident leprosy patients in vaccinated and unvaccinated populations over a number of years. Some/all of the above steps have been followed by various groups of researchers. In many cases, the ultimate test, the population study is under way and as yet the results are not available. As of to day apart from BCG, no other vaccine is available. All that we have are "potential or candidate vaccines". As expected all the candidate vaccines are first generation mycobacteria based. These are:

BCG

Based on the early observations that

BCG vaccination was able to induce lepromin positivity in lepromatous patients,[5] studies have been undertaken in several field laboratories across the globe. Fifty to 80% protective efficacy of BCG has been reported in studies undertaken in Uganda,[6] Papua New Guinea,[7] and Malawi.[8] In contrast the efficacy of BCG, in a similiarly conducted trial by WHO in Burma,[9] was found to be only marginal (around 20%). The variations in the results have been attributed to racial differences, susceptibility to disease, age at inoculation, influence of environmental mycobacteria, strain variation (Danish/Pasteur) etc.[10,11]

An opportunity arose in south India, where BCG had been given to a very large population to study its effect in prevention in tuberculosis.[12] Here, the two strains of BCG (Danish and Pasteur) had been given for comparison also. Published results, relevant to leprosy prevention indicate, a lower protection (17 to 24%) with use of single dose of BCG.[13] Protection was highr when larger dose (0.1mg) of BCG was used as compared to one tenth the dose. It was observed that the efficacy was better in the younger age groups. Further, no difference in response was observed in those who were initially PPD positive or negative. Likewise no difference in the clinical type of disease in the vaccinated and unvaccinated groups was seen. In short, this large scale BCG trial in an endemic population with predominant non-lepromatous disease showed 20% efficacy against leprosy, the protection being more in uninfected (younger population), no decrease in smear positive cases in vaccinated group and not much difference in outcome with the two strains of BCG.[14]

It is thus seen, that protection with single dose of BCG against leprosy has varied from place to place and ranged from 17 to 80% one thing being clear that when given early in childhood, protection was somewhat better.

For prevention of tuberculosis, several Latin American countries continue applying repeated BCG vaccination in the population. In fact, repeated BCG vaccination has been used as a leprosy control measure for many years in Venezuela. The policy has been to vaccinate all household contacts with repeated doses of BCG until a positive lepromin response develops. As part of the investigation, Convit and his colleagues,[15] have studied the relationship of number of BCG scars with leprosy protection and found a posititve correlation in a large case control study. Researchers from Malawi, have extended the work. The authors have conducted randomized, double blind trial to compare the protection afforded by one versus two doses of BCG vaccine.[16] Almost 50 percent reduction in number of new post vaccination leprosy patients was observed in the group given two doses as compared to one during follow up period of 5 to 9 years. Earlier in this region, one dose of BCG had itself been shown to give 50% protection when compared with placebo. This indicates that 2 doses of BCG were effective in leprosy prevention to the tune of almost 70%. As in earlier studies, here also the protection was greater among younger than older age group, suggesting that protection imparted by BCG is better when given before infection with other environmental mycobacteria. These findings suggest utility of 2 doses

of BCG in leprosy prophylaxis.

M.leprae+BCG

Way back in 1974, Convit and his associates had demonstrated that lepromatous patients responded with competent granuloma formation locally when injected with mixture of BCG and killed M.leprae and that there was a complete clearance of mycobacteria locally within 3 to 4 weeks of infection.[17] This was suggested to be on account of immune stimulation and macrophage activation locally. It was hypothesized that vaccine preparation that has therapeutic effects, as above in lepromatous patients, who have specific immune unresponsiveness, should effectively induce protection in healthy population.[18,19] Based on this, trials with combination of BCG+killed M. leprae were undertaken.[20] Fortunately, by then large quantities of M.leprae from armadillo became available.[21]

Results of the study, conducted in 29,113 contacts of leprosy patients, revealed no significant difference in the number of incident cases in the groups given BCG alone or BCG+killed M.leprae.[22] Even in the subgroup of interest i.e. those who were initially SPA negative and in whom disease was diagnosed more than one year after vaccination (as the earlier disease could have been missed/disease was erupting) only 18% fewer cases were observed in BCG+killed M.leprae group. There was no difference in total population figures during the five year follow up period.

Studies on similar lines have been undertaken in Malawi also.[16] Two groups of population, without and with earlier BCG scar, were randomized into subgoups. Scar negative individuals were given BCG alone or BCG+killed M.leprae, while the scar positive population received either placebo, BCG or BCG+killed M.leprae. The population has been followed up for 5 to 9 years for incident leprosy cases. Results have indicated that addition of killed M.leprae to BCG does not add to any protective efficacy of the latter irrespective of the fact whether M.leprae is added to first or repeat BCG vaccination. Fewer cases were observed in those who had an earlier BCG scar than in the first group.

Thus, work from both Latin America and Africa clearly bring out that the addition of killed M.leprae does not add to the protective value of BCG and at the same time reenforce the utility of BCG, more so when repeated inoculations are given.

ICRC vaccine

This mycobacterium was isolated from human leproma in 1958,[23] and had been passaged many times in artificial media by Bapat and his colleagues, working at Indian Cancer Research Institute, Mumbai. Strain C-44 was found to cross react with M.leprae and has been used for making vaccine.[24] Taxonomical studies suggest that the organism is not M.leprae and belongs to Mycobacterium avium intracelluar group.[25] Work has shown that not only is the organism able to stimulate depressed T cell function of PBMC from lepromatous leprosy patients in vitro,[26] but is also able to suppress multiplication of M.leprae in mice,[27] as also elicit positive skin test response in lepromatous patients.[28]

Studies conducted with vaccine pre-

pared from irradiated (killed) ICRC bacilli have shown it to enhance T cell reactivity,[29] and induce lepromin conversion in persistently lepromin negative lepromatous patients.[30,31] Clinical reversal reaction, faster clearance of M.leprae together with histological upgrading (epitheloid cell collection) have been reported in a proportion of patients.[32] These findings have led to the initiation of immunoprophylactic studies in Osmanabad, Latur and Sholapur districts of Maharashtra.[33] Beginning in February 1987, half of the randomized 30,000 contacts have been given irradiated ICRC vaccine while the remaining half received BCG. Follow up is being continued. Results are yet not available.

In the meantime, assessments have been made to find out the sensitization potential of ICRC vaccine even though this is not a very definite index of disease resistance. Results have demonstrated that the vaccine possesses a significant sensitizing effect as indicated by positive post vaccination response to MLSA and lepromin suggesting possible protective role.[34]

Mycobacterium w.vaccine

Talwar and his associates from New Delhi, have tried to break M.leprae specific immune tolerance of lepromatous patients by using antigenically cross reactive mycobacteria. They screened 15 standard strains of mycobacteria,[35] and could short list 5 organisms whose LTT and LMIT response was similar to M.Leprae.[36] These five (M.w.,ICRC bacillus, M.Vaccae,M. gordonae, M.phlei)were then used in preparation of lepromin like reagent and skin tested in patients across the spectrum.[28,37]. They observed that M.w. had the required cross reactive antigens, as demonstrated by positive skin tests in TT patients and possessed antigens which could provoke immune responsiveness in lepromatous patients. This saprophytic, cultiviable organism was then developed as potential vaccine.[25]

Initially this vaccine had been used as immunotherapeutic agent in lepromatous patients,[38] and in lepromin negative contacts.[39] Over half of the lepromatous patients showed conversion to lepromin positivity, and earlier skin smear negativity. A significant proportion of patients showed clinical and histological upgrading and even earlier granuloma resolution.[39] Repeat studies, with bigger sample carried out in 2 hospitals in Delhi, have confirmed the earlier observations.[40-43]. Independent work comparing the efficacy of M.w.vaccine with BCG showed similar efficacy of the two vaccines in lepromatous patients.[44]

Encouraged by these findings, the vaccine has been applied in the field (Kanpur) to test its immunotherapeutic utility and its prophylactic value against leprosy.[45] Follow-up is being continued and the results are expected in a year's time.

Other experimental vaccines

Singh and his fellow scientists, from Lucknow, have shown that another mycobacteria, M.habana (M.simiae serovar 1) protects mice against infectious challenge with M.tuberculosis (H37Rv), M.leprae, [46,47] and M.ulcerance. The organisms generates a cell mediated immune response which recognizes M.tuberculosis and M.leprae antigens and shares many antigenic proteins with them,[48,49],

an essential property required for an effective vaccine. Further, the organism (live, heat killed and gamma irradiated) has been shown to generate DTH response in mice against challenge with lepromin and habanin.[50] Whereas, the initial work is promising, toxicological studies, its effect in boosting/inducing CMI in lepromatous patients is still to be looked into before, it could even be called a candidate vaccine.

Stanjord and his associates (from U.K.) have been working with M.vaccae.[51] Based on skin test response and mice studies, wherein protective role has been shown, M.vaccae alone or in combination has been tested as immunotherapeutic agent. Results show some promise as faster bacillary clearance and upgrading was seen in histology.[52] Field studies on immunoprophylaxis are yet to be undertaken.

The results available so far indicate that BCG offers some protection against leprosy especially when given in multiple doses. Addition of M.leprae does not add to the protective value of BCG. Variability of racial and geographical variation of protection afforded by BCG both for tuberculosis and leprosy is well known. Therefore, study has been initiated in India (Chinglepattu district of Tamil Nadu) under the auspices of Indian Council of Medical Research (ICMR), not only to test the efficacy of BCG in Asian (Indian) population but also make a comparison of prophylactic value of available candidate vaccines in the same population and under similar conditions. This large well planned study has five groups-BCG, killed M.leprae+BCG, killed ICRC bacilli, killed M.w. and a placebo with almost 60,000 subjects in each arm,[53,54] Five year follow up of the population is almost over, results may be available soon.

One of the major problems likely to be encountered in this well planned trial, as has also been experienced in other studies, is the small number of incident cases that are likely to be seen. Following MDT application, the incident rates have begun to show decline, although slowly. Therefore, we may have less than expected number of patients in each group making statistical comparison more difficult. Another more relevant issue is the difficulty in estimation of protection against serious forms of disease consequent to early detection and treatment. Further clustering of leprosy cases (at regional/village/household level) may influence the outcome especially lin South Indian trial as prevalence figures vary from 1 to 36 per 1000 between villages/hamlets.

Second generation vaccine

Available results indicate potential of BCG as vaccine. It is considered that this may be on account of the fact that it has live organisms which continue to release stimulatory antigens over long periods. Scientists have been working on protective cell wall proteins and some potentially protective cell wall protein antigens of M.leprae have been identified. Approaches have been developed to introduce genes coding for these protective antigens into BCG.[55] The effect of such modified BCG on cytokine liberation is being studied.

Attempts are also being made to intro-

duce several protective protein genes from diverse organisms in BCG simultaneously with the aim of developing a vaccine which will give protection against many diseases including leprosy, tuberculosis, typhoid and viral infections etc, a futuristic research approach. Considering that a vaccine does become available in the near future, which is effective in preventing leprosy, the question of feasibility of its application in the field will have to be dealt with. One or multiple injections, the storage, the distribution, the expertise, the cost involved, the danger of viral infections getting transmitted etc. will all have to be looked into. Another aspect of concern is what would be the acceptability of the vaccine, can an immunoprophylactic agent be selectively applied in the field e.g., to contacts only, to children only, to special groups of individuals or localized areas etc., the planners and the administrators will certainly find the answers difficult. Another concern will be the safety of vaccines on long term basis with particular reference to adjuvant arthritis secondary to inoculation of large amounts of mycobacteria. Finally, would there be a need for vaccine in future? If the data/figures available from WHO/NLEP, and the projections made thereof, are to be taken seriously, there may hardly be any role for vaccine 5 to 10 years hence. Despite all this, continued pursuit on vaccines in leprosy is a not fruitless exercise. The vaccines, any for that matter, appear to be useful in highly bacillated BL/LL patients who do not show bacterial clearance at the usual pace, in the reducing problem of persisters (and possibly resisters) and relapses thereof in long run.

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