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Anti-leprosy vaccines: current status and future prospects.

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Abstract

Different types of leprosy vaccines are currently used in field trials in India. The rationale behind their use, the parameters for determining their efficacy, their merits and demerits are discussed and the future prospects are highlighted.

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Full Text

:: Introduction

The word 'vaccine' is derived from the French 'la vacche' meaning the cow, a reference to the cowpox extract used by Jenner in 1812 to prevent smallpox in humans. Pasteur introduced the concept of attenuated vaccines. Vaccines act by enhancing host immunity and are, perhaps, the most effective means of controlling infectious diseases. The global eradication of smallpox could be achieved mainly because of the availability of a cheap and effective vaccine.

Generally, vaccines are prepared by using the killed or attenuated organisms that have lost their virulence but have retained their 'protective' antigens. A second option is to use a live attenuated or killed non-pathogenic organism that antigenically cross-reacts with the pathogen. A third approach would be to use only the immunogenic 'subunit(s)' of the organism. All the three approaches have been used in the preparation of a 'candidate' anti-leprosy vaccine[6],[9],[13],[35] [Table:1].

In India, the second option of using antigenically related cultivable organisms is being actively pursued[5],[12],[13] [Table:2].

A vaccine containing ICRC bacilli (which are cultivable leprosy derived mycobacteria probably belonging to *M. avium intracellulare* complex) was prepared in 1979 at the Cancer Research Institute, Mumbai[12]. Studies, both on humans and animals, show that the ICRC bacilli exhibit antigenic cross-reactivity with *M.leprae* with reference to both B and T cell antigens[8],[19],[20],[27]. The capacity of a large number of T4 + clones, developed from a patient of tuberculoid leprosy, have been tested in response to *M.leprae* soluble protein[17]. The reaction of several clones with ICRC bacilli suggests a close relationship with *M.leprae* with reference to T cell antigens. Studies also show that the antigens of the ICRC bacilli are also more accessible, making the organism a stronger immunogen.

One of the first vaccines to be used against leprosy was BCG. BCG was found effective against the growth of *M.leprae* in foot-pads of mice[30]. However, trials with the BCG vaccine on human beings at four major places showed varied results[18]. In Uganda, a protection of 80% was observed, while that in Papua New Guinea was 46%. Trials in South India showed 28% protection and in the Burmese trial, it was 20%. Thus, it has been concluded that the protective effect of BCG has generally been modest, except in Uganda. By itself, BCG vaccination is no more considered to be a modality for immunoprophylaxis of leprosy.

Although *M.leprae* is yet to be cultivated, it grows profusely in armadillos[25]. Convit et al showed that the immunogenicity of *M.leprae* (which is a weak immunogen) is enhanced by the addition of BCG[10] and subsequently established the concept of a mixed vaccine containing a mixture of heat-killed armadillo-derived *M.leprae* (*M.leprae*-A') + BCG. The mixed vaccine induces immunological changes both in leprosy patients and in health persons but either organism given alone is ineffective. No information is available on the stability of the immune conversion and on antigenic variation, if any, between *M.leprae* obtained from different armadillos. This mixed vaccine is currently undergoing trials in Venezuela and Malawi.

A vaccine prepared from *Mycobacterium welchii (M.W.)* has been shown to induce lepromin conversion in BL/LL patients[5]. *M.W.,*a rapid growing mycobacterium is said to be a cultivable saphrophytic soil bacillus[14]. The vaccine has been used in patients with multibacilliary leprosy and the results are similar to those obtained with the ICRC vaccine[12],[36]. But this should not be surprising because ICRC and M. W. are similar with reference to cell antigens[20],[27].

Scientists at the Central Drug Research Institute Lucknow have shown CMI response in mice M and in langur and rhesus monkeys[14] using a vaccine prepared from *M.habana,* a photochromogenic atypical mycobacterium.

Stanford *et al* have demonstrated lepromin conversion in humans using a mixed vaccine containing BCG and killed *M. vaccae*[32].

According to Mahadevan *et al,* the lipid component of cell wall of *M.leprae* prevents the recognition of bacilli by macrophages and is thus responsible for anergy seen in LL patients. However, patients with TT leprosy exhibit CMI response due to high levels of serum lipase, which removes the lipids of the cell wall. Delipidified cell component (DCC) of *M.leprae* have been shown to activate macrophages and kill *M.leprae* in vitro[29]. Its safety and toxicity studies are in progress.

Parameters For Determining Vaccine Efficacy:

The ultimate of any vaccine is determined by its ability to lower the incidence of the disease. Leprosy is a disease with a long incubation period and therefore, such studies would take many years to complete. Before such long term large scale field studies are initiated, it would be essential to show, both in experimental and clinical studies, that the 'candidate' vaccine is capable of effecting immunological changes that portray 'protective' immunitly. In the present state of our knowledge, cell mediated immunity (CMI) is the dominant host defence against *M.leprae* and circulating anti-*M.leprae* antibodies have little role.

Much of the vaccine development in leprosy is based on response to skin tests with soluble and integral (Mitsuda) antigens of *M.leprae*[16]. Though the relationship between skin response and protective immunity is yet to be established, among the available tests, the Mitsuda test correlates best with the capacity of the host to handle *M.leprae*, while the lymphocyte transformation test (LTT) is not considered a good index of protective immunity[3]. On the other hand, the Mitsuda test is also a good indicator of host susceptibility in armadillos[22] and monkeys[34] - the two species that develop disseminated *M.leprae* disease. Mitsuda negative individuals living in endemic areas run a high risk of contracting multibacillary forms of leprosy[15] and in untreated patients, the Mitsuda test is inversely related to the tissue bacillary load[28].

Leprosy is a spectral disease in which the clinical and pathological features reflect the CMI of the host[28]. There is a progressive improvement in CMI and a reduction in the tissue bacillary load from the lepromatous (LL) to the tuberculoid (TT) end of the spectrum. 'Upgrading' in the spectrum, therefore, indicates improved CMI. A candidate vaccine should be able to induce 'upgrading' in the anergic LL patients and bring about lepromin conversion in both the patients and lepromin negative healthy sibjects. Ideally, a candidate vaccine should also show protection in animal models. However, there are no suitable animal models for leprosy. From the data presented at the Pre- congress Workshop on 'Leprosy Vaccine Trials' held under the auspices of the XIII International Leprosy Congress at The Hague in September 1988, it was clear that the studies on mouse foot- pads (the most widely used laboratory model) have given variable results in different laboratories with reference to all candidate vaccines (Sengupta, U., Personal communication).

From The Laboratory To Large Scale Field Studies:

Studies with the ICRC vaccine since 1979 show that a single dose of the vaccine brings about persistent immune conversion in 53% of LL patients on chemotherapy, associated in some patients with 'upgrading' of tissue reaction and accelerated clearance of bacilli from the tissues of the patients[12],[13]. About 10% of the patients had post-vaccination reversal reactions[1] and about a third of the patients with a high bacillary index developed ENL 10-15 days after vaccination[12]. Despite the upgrading, no fresh nerve lesions were observed in the vaccinated patients [12],[13]. Similar findings have been reported by Convit *et al,* in their studies[9],[10]. The ICRC vaccine induces immune conversion in 95% of lepromin-negative healthy sibjects in endemic areas[4] and the conversion was found to be stable for 5 years. These clinical observations are supported by the results of studies carried out in our monkey mode[7].

Until 1984, the vaccine had been tried only on LL patients and lepromin-negative healthy persons. However, in large scale field studies, the vaccine would have to be administered to volunteers without subjecting them to a pre-vaccination lepromin test. Thus, the target population would include both lepromin positive and negative individuals, which would be a sub-set of the general population. Hypersensitivity to *M.leprae antigens, to which the residents of an endemic area are exposed continuously, has been implicated in the pathogenesis of nerve damage in leprosy*[21],[33]. Lepromin positive vaccines could be at a major risk of developing neural lesions since they already possess a strong CMI to the antigens of *M.leprae.* But such fears have been allayed by the results of the pilot study, which was conducted under field conditions, about 100 kin from Mumbai. No untoward effects have been observed during the last 4 years in both lepromin positive and negative healthy household contacts (HHC) of multibacillary leprosy patients, who were given the ICRC vaccine[4]. The vaccine is safe and well tolerated and its

acceptability is high since it is given as a single dose. This vaccine has no effects on antibody levels[4]. Circulating anti-*M.leprae antibodies have little role in host defence against leprosy, but these have been implicated in certain Hyperseitsitivity reactions*[12],[33]. Antibodies could also form immune complexes that might suppress CMI. As the ICRC vaccine is developed from a cultivable organism, it will be cheap and there will be no chance of contamination with animal products. This vaccine also induces stable immunity unlike vaccines that contain armadillo-derived *M. leprae.*

The large scale field studies of the ICRC vaccine were launched in February 1987 in south-eastern part of Maharashtra [Figure:1]. The prevalence rates for leprosy in this area vary between 8 to 10 per thousand. The studies are randomised, controlled and involve HHC of leprosy patients. A comparative evaluation of the two mycobacterial vaccines (ICRC and BCG) will be made by measuring the incidence of all forms of leprosy in the vaccines. The vaccines are of both sexes between 1 and 65 years of age. Pregnant women, and persons with chronic debilitating diseases, severe malnutrition history of allergic reactions, epilepsy and tuberculosis are excluded from the studies. On the basis of the list of leprosy patients provided by the Leprosy Control Units of the Government of Maharashtra, the patients are visited on a house-to-house basis and only house hold contacts (HHC) of patients with signs of active disease participate in the programme. Simultaneous to the clinical examination, the vaccines are given randomly to the eligible HHCs, intradermally in the right deltoid region. Both vaccines produce a comparable local reaction consisting of delayed inflammation and ulceration that heals in 4-6 weeks. No systemic reaction in usually seen.

The sample size for the two-arm study with a five-year follow-up would be 31,000. The intake has been completed. The vaccines would be followed-up for 10 years.

:: The future

The science of vaccinology has come a long way from the 'first generation' vaccines that contain the whole organism [Table:1]. The whole organism, attenuated or killed, may contain some antigen(s) that may be immunosuppressive, making the vaccine less effective. Moreover, such a vaccine may produce undesirable side effects. These problems could be overcome by using only the 'protective' immunogenic 'sub-unit'. It is now recognised that the immunogenicity of a protein molecule resides in segments of its small peptides[22]. A vaccine containing only the peptide possessing the specific immunogenic epitopes will be 'purer' and such peptides could be synthesized chemically or biosynthesized using recombinant DNA technology.

So far, *M.leprae* has resisted attempts at cultivation and this could be limiting factor in preparation of large quantities of a 'sub-unit' vaccine. Using recombinant technology, the entire genome of *M.leprae* has been cloned[35]. Recombinant DNA clones containing gene coding for 5 immunogenic proteins have been isolated using monoclonals. If scientists succeed in identifying the 'protective' antigen(s) from amongst these proteins, the non-cultivability of *M.leprae* would no longer be a constraint since the clones making 'protective' antigen(s) could be a constant source of supply for the preparation of a vaccine.

Scientists at the Cancer Research Institute, Mumbai, have adopted the alternative strategy of fractionation of the sonicate of ICRC bacilli to identify its immunogenic 'subunit(s)[6],[8]. On high Performance Liquid Chromatography using gel permeation columns, the sonicate yields a very high molecular weight fraction (approx. 1 million daltons) named PP-1, which is the dominant T-cell immunogen of the ICRC bacilli[8]. A similar fraction has been isolated from the sonicate of *M.leprae.* The PP-I fractions of the two organisms exhibit antigenic cross- reactivity. PP-I is a glycoprotein and is probably a component of cell walls. Recently, a very high molecular weight cell wall core (CWC) fraction has been isolated from *M.leprae.* CWC is also a strong T-cell immunogen[23]. A vaccine containing PP-I of ICRC bacilli induces lepromin conversion in lepromatous patients and their lepromin-negative HHC[2],[6]. Being a glycoprotein, PP-I contains all the components essential for vaccine. Its proteins could act as antigens or carriers for carbohydrates or lipids which could by themselves act as antigens. In addition, the lipids would also provide a built-in adjuvant. This vaccine containing PP-I of ICRC bacilli is currently undergoing Phase-I and II clinical studies in India.

Leprosy and tuberculosis are the two dominant mycobacterial diseases that are major health problems in the Third World. Mycobactetium avium intracellulare group of organisms have acquired a special significance in developed nations too, because of their frequent isolation from AIDS patients[24].

Since the ICRC bacillus belongs to the *M.leprae* intracellulare (MAI) complex, the vaccine may also act against infections caused by these opportunistic microbes[11]. A mixed vaccine containing BCG and ICRC bacilli or their immunogenic 'sub-units' could be the future polyvalent mycobacterial vaccine that might offer protection against a wide spectrum of mycobacterial diseases. Such a polyvalent mycobacterial vaccine would reduce the number of vaccinations and thus would be of tremendous operational advantage to health authorities especially in the Third World.

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