Vaccination

A candidate anti-leprosy vaccine from ICRC bacilli

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Two approaches, namely the use of armadillo-derived *M. leprae* or cultivable mycobacteria antigenically cross reacting with *M. leprae*, have been generally followed in preparation of anti-leprosy vaccines. The ICRC anti-leprosy vaccine belongs to the second category. The ICRC bacilli are a group of leprosy-derived cultivable slow growing mycobacteria belonging to the *M. avium intracellulare* complex. The organisms exhibit antigenic cross reactivity with *M. leprae* both with reference to T and B cell antigens including with *M. leprae* specific monoclonals WML03 and WML10 (Deo, 1989).

The vaccine has been in use since 1979. During this period, the phase-I and II clinical trials, in which the vaccine has been administered to about 100 LL patients on chemotherapy, and 50 healthy lepromin-negative subjects, have been completed. A single dose of the vaccine brings about immune (lepromin) conversion in about 53% of the patients associated, in some patients, with "up-grading" and tissue bacillary clearance. Reversal reaction with granulomas exhibiting BT lesions is observed in 8% of the patients. About 30% of the patients with BI 3 + and above develop ENL 10–15 days post-vaccination. Despite the "up-grading" no fresh nerve lesions are observed. High conversion rates (about 95%) are observed in lepromin-negative healthy residents of endemic areas.

Results of the ICRC vaccine, both in patients and healthy persons, compare well with those obtained by Convit et al. (1983). However, in their studies, the immune response wanes progressively (Workshop report, 1989). Immune conversion induced by ICRC bacilli is stable for 5 years in the LL patients. Being developed from a cultivable organism, the ICRC vaccine has the advantage that it would be readily produced in large quantities at a cheap rate. Further, unlike the vaccines containing *M. leprae* A, the ICRC vaccine carries no risk of contamination with animal products.

Zaheer et al. (1989) have also obtained similar results with a vaccine containing a cultivable organism Mycobacterium w (Mw). But this should not be surprising because the two organisms (ICRC and Mw) are similar in many respects (Table 1). They shows similar extent of DNA homology with *M. leprae* DNA and give identical RFLPs with DNA probes (Grosskinsky et al., 1989).

Table 1 Comparative Features of ICRC and Mw

Isolation	ICRC 1958	Mw (1978)
Taxonomical classification	MAIS (Shepard, 1983, personal communication, Stanford, 1989)	MAIS
Cultural and growth characteristics	Two cultures (ICRC and Mw) behave very similarly on bacteriological media and have a temperature optimum for growth of 35 °C (Shepard, 1983, personal communication)	
Antigenic relatedness	Identical for the two organisms (Stanford, 1979, personal communication)	
Host Response		
LTT	Very similar (Mustafa & Talwar, 1978)	
Skin reaction	Very similar (Sahib and Vallut, 1973)	
DNA Homology		
M. leprae	Identical (Grosskinsky et al., 1989)	
RFLPs (Pst-I and BESt-II and *M. leprae* 3.6 Kb EcoRI and *M. tuberculosis* 65 kDa antigen gene probes	RFLPs with both enzymes and probes identical for ICRC and Mw (Grosskinsky et al., 1989)	

MAIS: *M. avium intracellulare scrofulacaeum* complex

So far, in all studies, vaccines have been given to patients on chemotherapy, which by itself induces bacillary clearance. Faster clearance observed by all workers could be due to non-specific stimulation of macrophages by the components of mycobacteria which are excellent adjuvants. This is substantiated by the fact that, in the patients, the vaccines have to be repeatedly administered. To prove that a vaccine has a specific immunotherapeutic action, it would be essential to try it in patients receiving no treatment. However, knowing the importance of drugs in treatment of leprosy, such human studies would be unethical.

We, therefore, followed a somewhat different approach of vaccinating LL patients who are "clinically" resistant to multi-drug therapy (MDT). These patients showed no clinical improvement or a drop in their BI despite 2–3 years of MDT. Ten such patients were vaccinated. On the basis of the response to the vaccine, they could be categorized into responders and non-responders. The mean BI in the responder-group, consisting of 6 patients, was 3.0 + and 1.7 − before and 6 months post-vaccination. One patient developed reversal reaction with BT granuloma. The non-responders, who had the average BI of 3.2 +, may represent a dinstinct sub-group of

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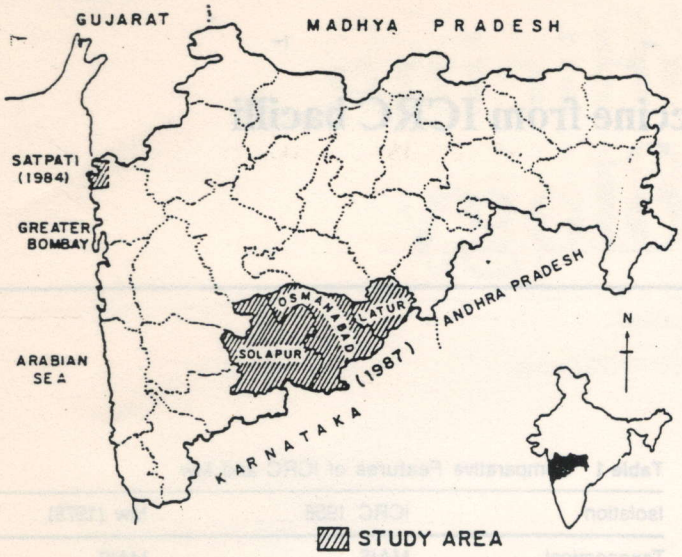

Fig. 1 Map showing trial area

LL patients non-responsive to the vaccine. But before drawing such conclusions, it would be essential to show that they do not respond even to a booster dose of the ICRC vaccine.

Until 1984, the vaccine was tried only on LL patients and lepromin negative subjects. In the large scale field trial discussed below, however, the vaccine is administered to volunteers without subjecting them to prior lepromin test. The target population would, therefore, include both lepromin positive and negative persons.

Hypersensitivity to *M. lepare* antigens, to which residents of endemic area are exposed continuously, has been implied in pathogenesis of nerve damage in leprosy. It was, therefore, feared that, on vaccination, lepromin positive individuals may develop nerve damage. But such fears have been set to rest by the results of the pilot study in which both lepromin positive and negative healthy house-hold contacts (HHC) of multibacillary leprosy patients were vaccinated five years ago and no untoward effects have been observed so far (Chaturvedi et al., 1987).

The large scale trial of the vaccine was launched in February 1987, in India, in the South-eastern part of Maharashtra (Fig. 1), where leprosy prevalence rates vary between 8 to 10/1000. The objective of the trial is to make a comparative evaluation of the immunoprophylactic efficacy of the two vaccines containing (a) ICRC and (b) BCG by measuring the incidence of all forms of leprosy in the vaccinated subjects. The trial is randomized, controlled and involves HHC of active leprosy patients. The vaccinees are of both sexes between 1 to 65 years of age. Pregnant women and persons with chronic debilitating diseases, severe malnutrition, history of allergic reaction, epilepsy and tuberculosis are not included in the trial. So far 30,000 HHC have been vaccinated. Sample size required for the two arm trial, with a five year follow-up, would be about 32,000. The vaccinated HHC would be followed for 10 years.

We have recently fractionated the sonicate of ICRC bacilli in order to identify its immunogenic sub-unit(s). On High Performance Liquid Chromatography, using gel permeation columns, the sonicate yields a very high molecular weight($MW-10^6$) fraction maned PP-I which is the dominant T-cell immunogen of the ICRC bacilli (Deo, 1989). 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, which is a glycolipoprotein, is probably a component of cell wall. Recently, Kaplan et al. (1988) have isolated a very high molecular weight cell wall core (CWC) fraction from *M. leprae*. The CWC is also a strong T-cell immunogen. A vaccine containing PP-I of ICRC bacilli induces lepromin conversion in patients and their lepromin negative HHC. The sub-unit vaccine is currently undergoing Phase-I and II clinical studies in India (Deo, 1989).

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