

Immunotherapeutic potential of ICRC vaccine: a case control study

W S BHATKI & R G CHULAWALA

Acworth Leprosy Hospital, Wadala, Bombay 400 031, India

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Summary A bacteriological follow-up of 16 lepromatous patients with a high initial Bacteriological Index (BI) showed that in 8 randomly selected patients who received single doses of ICRC Vaccine (C44) at the onset of multidrug therapy, the average reduction of BI was from 4·4+ to 1+ in 2 years—3 of these patients became negative and 3 showed BI 1+ or less. Comparable bacteriological assessments in 8 non-vaccinated but otherwise similar patients showed an average reduction of BI from 4·7+ to 2·6+, i.e. consistent with the expected response to MDT in lepromatous patients. Here we discuss the role of immunotherapy and the selection of a desirable antileprosy vaccine in the context of fixed-duration MDT.

Introduction

Rapid bacterial clearance from skin smears and histopathology sections have been reported in patients given ICRC Vaccine.^{1,2} However, these observations were made on patients who had not been standardized by classification, drug regimen and duration of past treatment and illness.

Multidrug therapy (MDT) based on rifampicin, clofazimine and dapsone (DDS), used at present for the treatment of multibacillary (MB) leprosy, kills viable *Mycobacterium leprae* rapidly. However, the fall in the Bacteriological Index (BI) in lepromatous patients on these drugs is at the rate of 0·6 to 1 Index per year, the same as patients who are on DDS monotherapy.³ Due to persistent bacterial positivity, MDT is often continued by clinicians for more than 2 years. It would therefore be advantageous to have a therapy which would not only kill the bacilli but also rapidly clear their debris.

In the present study, the ICRC Vaccine was used to see if it could supplement conventional MDT to achieve early bacillary clearance.

Methods and materials

The present study included 16 lepromatous patients (13 males and 3 females) admitted to the Acworth Leprosy Hospital, Bombay.

Table 1. Average pretreatment BI of both groups and after 1 and 2 years' treatment

	No. of patients	Average BI		
		Pretreatment	1 year treatment	2 year treatment
Group I (Vaccinated patients)	8	4.4+ (SD=0.69)	2.8+	1+ (SD=1.29)
Group II (Control patients)	8	4.7+ (SD=0.46)	3+	2.6+ (SD=0.84)

Pretreatment BI—Group I *vs* Group II: $t=1.18$, $p>0.05$ (not significant).

2 year treatment BI—Group I *vs* Group II: $t=2.58$, $p<0.05$ (significant).

All these patients had active, disseminated, infiltrating lesions with occasional nodules. The skin smears, collected by slit and scrape method, from at least 2 sites, including 1 earlobe, showed a BI of 4+ to 6+ (Ridley's scale). From the patients without obvious thick infiltration and nodules, additional smears were collected from 1–2 additional sites, including the other earlobe. The classification was further confirmed by skin biopsies which showed histology to be consistent with LL leprosy. All the patients were late lepromin reaction negative.

A total of 10 out of the 16 patients had no past history of any treatment, while 6 patients had received dapsone monotherapy with gross irregularity for periods of 3 months to 1 year in the preceding 3 years.

The patients were randomly divided into 2 groups of 8 patients each. Their initial BI was as follows:

Group I —1 patient = 6+, 4 patients = 5+, 3 patients = 4+
(18 smears, Average BI = 4.4+, SD = 0.69)

Group II —1 patient = 6+, 5 patients = 5+, 2 patients = 4+
(19 smears, Average BI = 4.7+, SD = 0.46)

All the patients were kept on daily supervised MDT along with other in-patients of the hospital, i.e. rifampicin 600 mg once a month, clofazimine 50 mg daily and dapsone 100 mg daily. All the patients were hospitalized throughout the 2 years and except for the few earlier patients the clofazimine 300 mg booster dose was given every month.

At the onset of therapy, the patients belonging to group I were given ICRC Vaccine (C44 strain, 1×10^8 bacilli/0.2 ml) as intradermal injection, 0.1 mg on each deltoid region. The ICRC Vaccine was obtained from the Cancer Research Institute, Parel, Bombay. The patients belonging to group II were given saline in a similar manner.

All the patients were clinically and bacteriologically monitored every 6 months. Skin smears were collected from most active lesions and from one of the earlobes and the slides were sent to the laboratory together with the slides from other in-patients on MDT.

The bacteriological results were analysed after completion of 2 years of therapy.

Results

The initial average BI of the patients (i.e. Group I (18 smears) = 4.4+ and Group II (19

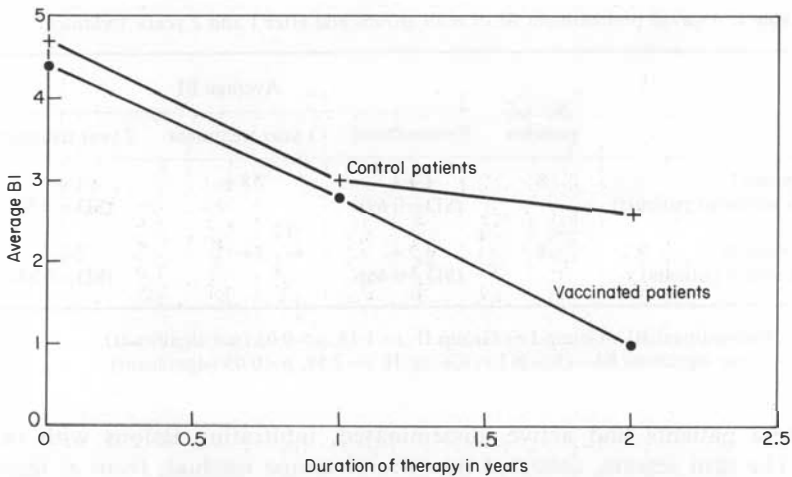


Figure 1. Average BI of vaccinated and control patients.

smears) = 4.7+) indicated that the 2 groups had comparable bacteriological status ($t = 1.18$, $P > 0.05$, Table 1).

Bacteriological responses observed in the patients showed that at the end of the 1st year, there was no significant difference in the average BI of the 2 groups (Figure 1). However, at the end of the 2nd year, the average BI in Group I (1+) was found to be significantly lower than that seen in Group II (2.6+), i.e. $t = 2.58$, $P < 0.05$ (Table 1).

For analysing the bacteriology of individual patients at the pretreatment stage and at the end of 1 and 2 years' treatment, the maximum BI reported in each patient was considered (Figure 2 and Tables 2 and 3). Analysis of patients' BI showed (Table 2) that in Group I, 3 out of 8 patients had become smear negative and 3 had a BI of 1+ at the end of 2 years' therapy. The corresponding BI in Group II showed that 5 out of 8 patients had a BI of 3+ or more. It is clearly seen that significantly higher numbers of ICRC vaccinated patients (i.e. 6 out of 8 patients from Group I) showed a BI of 1+ or less than control patients (i.e. none out of 8 from Group II).

Bacteriological response of individual patients in relation to their initial BI (Figure 2, Table 3) showed that the 3 patients from Group I who became smear negative in 2 years had an initial BI of 4+. In comparison 2 patients with an initial BI 4+ from Group II, however, showed BI 2+ and 3+ at the end of 2 years' therapy. The patients with an initial BI 6+ showed falls to 1+ and 3+ in Groups I and II, respectively. The patients with initial BI 5+ showed that in Group I 3 out of 4 patients showed a BI 2+ or less while in Group II, 3 out of 5 patients had BI 3+ or more after 2 years' therapy. This shows that the fall in the BI was related to the initial BI and it was comparatively faster in the ICRC vaccinated patients on MDT.

Discussion

Antileprosy drugs presently used for multibacillary patients kill *M. leprae* and render them nonviable in 1–3 months³ but their ultimate clearance from the body depends upon

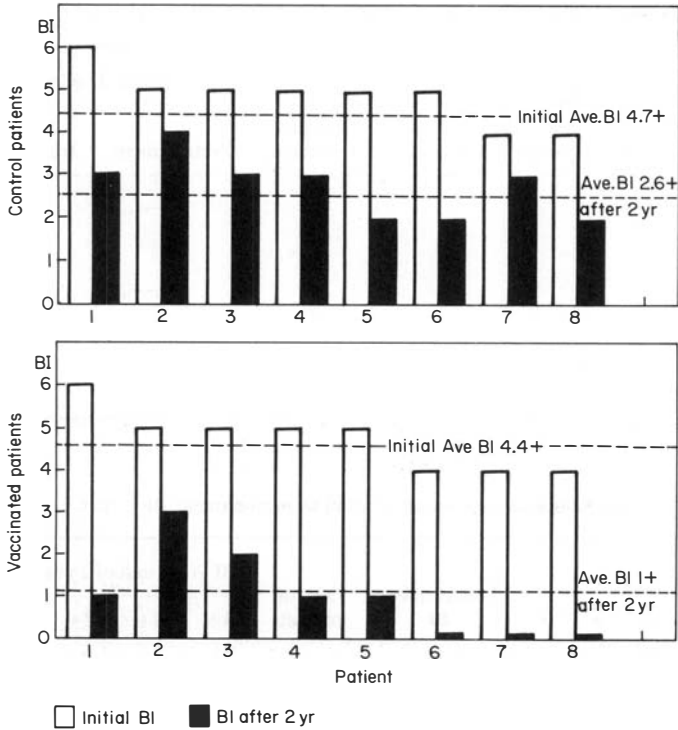


Figure 2. BI—initial and after 2 years of individual vaccinated and control patients.

the status of immunity. Thus skin smears bacteriology in the patients on MDT shows a lowering of the Morphological Index (MI) to 0% much earlier, while the BI continues to remain high for a much longer period.^{4,5}

According to the Government of India Guidelines on MDT, the treatment should be continued for 2 years or till smear negativity.⁶ Kiran Katoch *et al.*,⁷ reported that for BL/LL patients, it took 5 years of regular MDT to bring down the average BI from 4.45+ to 0.03+ with 86% patients showing smear negativity. It is also reported that in the initially highly bacillated BL–LL patients, viable bacilli are present in 9–16% tissue biopsies even after 2 years of MDT.⁸ On the other hand, in multibacillary patients, the relapse rate after 2 years of MDT is very low in spite of persisting BI³. We (in unpublished observations) and other experienced leprologists (personal communication) have observed that the BI continues to fall progressively even in the absence of any therapy beyond 2 years, thus supporting fixed-duration therapy. In the midst of these confusing reports, the clinicians in the routine MDT programme will never have enough confidence to stop MDT after 2 years in patients with BI 3+ or 4+. The morale and the enthusiasm of the control team would increase if their therapy was able to clear substantially bacilli from the skin smears in about 2 years.

Earlier reports on various antileprosy vaccine candidates suggested that the ICRC, MW and BCG with *M. leprae* have immunotherapeutic values because besides inducing lepromin conversion, they were able to bring about faster bacterial clearance and induce

Table 2. Distribution of patients according to BI

BI	Group I (Vaccinated patients)			Group II (Control patients)		
	Pretreatment	1 year treatment	2 years treatment	Pretreatment	1 year treatment	2 years treatment
6+	1			1		
5+	4			5	1	
4+	3	2		2	2	1
3+		2	1		3	4
2+		3	1		2	3
1+			3			
0		1	3			
No. of patients	8	8	8	8	8	8

Table 3. Bacteriological response in relation to pretreatment BI

	Pretreatment BI	No. of patients	BI at the end of 2 year treatment				
			4+	3+	2+	1+	0
Group I (Vaccinated patients)	6+	1				1	
	5+	4		1	1	2	
	4+	3					3
Group II (Control patients)	6+	1		1			
	5+	5	1	2	2		
	4+	2		1	1		

reversal reactions in BL–LL patients.^{1,2,9-11} Though these studies require wider multicentric trials with proper case control as regards past treatment, duration of illness, classification, initial BI etc, all the reported evidence since 1980 suggests that antileprosy vaccines do have a place in the therapy of leprosy.

The present case-control study, though based on a small sample of 16 lepromatous patients, certainly shows that ICRC vaccine given as a single dose is synergistic with the conventional MDT, and 6 out of 8 ICRC vaccinated patients showed a lowering of BI from 4–6+ to 1+ or less (3 patients were smear negative) within 2 years of therapy as against none out of 8 comparable lepromatous patients on MDT only (Table 2).

The bacteriological followup showed a significant difference in the average BI of vaccinated and non-vaccinated patients in the 2nd year of therapy but not in the 1st year (Table 1, Figure 1). This is quite consistent with our past experience with ICRC vaccine. Earlier trials showed lepromin conversion in a considerable number of patients as late as 8–12 months after vaccination.^{1,2} Furthermore 3 out of the 5 ICRC vaccine-induced reversal reactions developed 12–15 months after vaccination.⁹ It was also observed in our earlier studies that lepromin conversions were more frequent among the lepromatous patients who had been treated for a long time and who had a low bacillary load, i.e. BI less than 3+.

In view of this, it is possible to postulate that the immunotherapeutic action of ICRC vaccine on bacterial clearance is exhibited only after the BI is reduced to around 3+ (which usually occurs by the second year of MDT). This also suggested that the vaccine will have to be used in combination with MDT and not as a replacement for MDT.

Thus it may be concluded that an antileprosy vaccine, if used with MDT, might significantly reduce the period of treatment, thus reducing the consumption of antileprosy drugs (which are often in short supply) and lowering the leprosy morbidity substantially. However, such a vaccine has to be safe, acceptable and easy to administer under field conditions. The vaccine that has prolonged activity following a single dose is preferable to those that have to be given frequently and in multiple doses.

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Potentiel immunothérapeutique du vaccin ICRC: une étude de cas avec témoin

W S BHATKI ET R G CHULAWALA

Résumé Un suivi bactériologique de 16 lépreux avec un index bactériologique (BI) initial élevé a démontré que chez 8 patients choisis au hasard, ayant reçu une dose unique de vaccin ICRC (C44) au début d'une thérapeutique multidrogue, la réduction moyenne de BI était de 4,4+ à 1+ en 2 ans; 3 de ces patients sont devenus négatifs et 3 ont présenté un BI de 1+ ou inférieur. Des évaluations bactériologiques comparables chez 8 patients non vaccinés, mais par ailleurs similaires, ont révélé une réduction moyenne du BI de 4,7+ à 2,6+, c'est-à-dire conforme à la réponse attendue à la thérapeutique multidrogue chez des patients lépromateux. Nous discutons le rôle de l'immunothérapie et la sélection d'un vaccin antilépreux satisfaisant dans le contexte de la thérapeutique multidrogue de durée fixe.

El potencial inmunoterapéutico de la vacuna ICRC: un estudio del control de casos

W S BHATKI Y R G CHULAWALA

Resumen Un estudio bacteriológico posterior de 16 pacientes lepromatosos con un elevado Índice Bacteriológico (IB) inicial demostró que, en 8 pacientes seleccionados al azar y tratados con una sola dosis de Vacuna ICRC (C44) al comienzo de la terapia multidroga, el promedio de reducción de IB fue de 4,4+ a 1+, en 2 años. Evaluaciones bacteriológicas comparables de pacientes similares no vacunados mostraron un promedio de reducción de IB, de 4,7+ a 2,6+ es decir, la respuesta que se anticiparía mediante terapia multidroga en los pacientes lepromatosos. Se discute el papel de la inmunoterapia y la selección de una vacuna antileprosa conveniente en un entorno de terapia multidroga de duración fija.