Lepr Rev (2000) **71,** 193–205

Reactional states and neuritis in multibacillary leprosy patients following MDT with/without immunotherapy with *Mycobacterium w* anti-leprosy vaccine

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Accepted for publication 8 May 2000

Summary A vaccine based on autoclaved *Mycobacterium w* was administered, in addition to standard multidrug therapy (MDT), to 157 untreated, bacteriologically positive, lepromin negative multibacillary leprosy patients, supported by a well matched control group of 147 patients with similar type of disease, who received a placebo injection in addition to MDT. The MDT was given for a minimum period of 2 years and continued until skin smear negativity, while the vaccine/placebo was given at 3-monthly intervals up to a maximum of eight doses. The incidence of type 2 reaction and neuritis during treatment and follow-up showed no statistically significant difference in the vaccine and placebo groups. The incidence of type 1 reaction (mild in most cases), however, was higher in the vaccine group ($P = 0.041$, relative risk ratio 1.79), considering LL, BL and BB leprosy types together, and considerably higher ($P = 0.009$) in LL type, probably because of confounding due to higher number of patients with previous history of reaction in this group. The occurrence of reactions and neuritis in terms of single or multiple episodes was similar in the vaccine and placebo groups. The association of neuritis and reactions, as well as their timing of occurrence (during MDT or follow-up), was also similar in the two groups, with more than 90% of occurrences taking place during MDT. The incidence of reversal reaction was significantly higher among the males in the vaccine group (34.5% versus 8.3%, $P = 0.019$). Patients with high initial BI (4.1–6.0) showed higher incidence of reactions (70.3%) as compared to those with medium (2.1–4.0) and low (0.3–2.0) BI where the reactions were observed with a frequency

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0305-7518/00/0071193+13 $1.00

of 56.1% and 38.8%, respectively. However, unlike reactions, neuritis incidence did not seem to be affected by initial BI to the same extent in the vaccine group, with frequencies of 35.3%, 36.3% and 25.9% in the three mentioned BI ranges. Overall, the vaccine did not precipitate reactional states and neuritis over and above that observed with MDT alone.

Introduction

Reactional states and neuritis constitute an emergency in leprosy, calling for quick attention and proper management, since delayed or inadequate management of neuritis may lead to impairments which could become permanent. Two types of reactional states are well recognized, type 1 (reversal) reaction and type 2 reaction (erythema nodosum leprosum). Type 1 reactions, usually seen in borderline leprosy, occur most frequently during the initial phase of chemotherapy and are associated with abrupt rise in host cell mediated immune response to mycobacterial antigen.[1] Type 2 reaction (erythema nodosum leprosum) affects mainly multibacillary leprosy patients of LL and BL types. In one study, over 50% of LL and about 25% of BL patients experienced type 2 reaction;[2] in another study from South India an incidence of 35% of type 2 reactions has been reported in LL and BL patients.[3] The pathogenesis of this symptom complex is the formation of immune complexes which are deposited in various body sites; these complexes comprise mycobacterial antigens, IgG or IgM antibodies and complement.[4] The profile of reactions and neuritis presented in this communication forms a part of large scale clinical trials of a vaccine based on *Mycobacterium w* bacilli, under evaluation for its immunotherapeutic effects as an adjunct to multidrug therapy (MDT), in the hospital-based trial in Delhi since 1987.

Materials and methods

VACCINE

The vaccine is a suspension of killed *Mycobacterium w* in physiological saline in the concentration of 10^{10} bacilli per ml (the details of the vaccine preparation have been reported).[5] The first dose comprised 1×10^{9} autoclaved bacilli in 0.1 ml. physiological saline (0.85% NaCl) while subsequent doses contained half the number of bacilli, i.e. 5×10^{8}. The vaccine was administered intradermally in the deltoid region using a 30G needle. A total of eight doses were given at 3-month intervals, over a period of nearly 2 years.

PLACEBO

One gram of micronized starch (Sarabhai Chemicals, Baroda, India) was dissolved in 100 ml of distilled water, autoclaved at 15 lb per inch pressure for 15 min and dispensed in sterile vials.

MULTIDRUG THERAPY (MDT)

In the initial phase MDT consisted of 2 weeks of intensive therapy with 600 mg of rifampicin, 100 mg clofazimine and 100 mg dapsone daily. Subsequently, the patients received the WHO

recommended regimen of 600 mg rifampicin and 300 mg clofazimine once a month, supervised, plus 100 mg of dapsone and 50 mg clofazimine daily, self-administered. The MDT was given for a minimum period of 2 years and continued thereafter till the skin smear negativity was attained.

SUBJECTS AND STUDY DESIGN

Permission of the Drug Controller General of India and Institutional Ethics Committee was obtained before initiating the study. Written consent from the subjects was obtained before inducting them in the trial. The enrolled subjects comprised of untreated, lepromin negative, bacteriologically positive, active cases of multibacillary leprosy belonging to LL, BL and BB types. The diagnosis was confirmed on the basis of clinical examination and histopathology. The patients were allotted to the vaccine and placebo groups in a randomized manner as per codes supplied by the statistician.[5] The clinical trials had two series. The initial series comprising 120 patients of multibacillary (MB) patients was single blind, where the vaccine codes were known to the Head of the clinic but not to the attending clinician. The second series of trials, comprising 300 multibacillary patients, was double blind, in which neither the evaluating agency nor the patients were aware of the identity of the injection administered. The vaccine codes were decoded in 1992. In this report, the data from both the series have been combined as the protocol followed for treatment and follow-up in the two series was similar and the parameters of monitoring were identical. The average period of observation (including MDT and post-MDT follow-up) for the patients was 8.48 and 8.63 years in the vaccine and placebo groups, respectively.

REACTIONAL STATES AND NEURITIS

The type 1, type 2 reactions and neuritis were recognized based on clinical features. An episode of type 1 reaction was considered on noting visible changes in the skin lesions marked by prominence, erythematous hue and a subjective feeling of warmth, associated with or without constitutional symptoms. Type 2 reaction was considered as an episode of systemic syndrome with fever, aches, bony tenderness, joint pains with or without specific involvement of any organ, e.g. eyes, kidneys, testis, also irrespective of appearance of characteristic lesions of erythema nodosum leprosum. An episode of neuritis was diagnosed on observing thickened tender nerves in the presence or absence of inflamed skin lesions. Peripheral nerves were examined for thickening and tenderness, superficial sensations (temperature, pain and touch) were tested using a temperature tester (supplied by WHO), pin and cotton wisp, respectively. Motor functions were assessed using voluntary muscle testing.[6]

In all three types of complications mentioned, only those episodes were considered for counting which required management with non-steroidal anti-inflammatory drugs, e.g. prednisolone, clofazimine. A proforma for leprosy reactions was filled in at the time of the patient's induction and subsequently during each reactional episode. The details of present and past history of reactional and neuritis episodes, presence or absence of constitutional symptoms like fever, malaise, pain or tenderness of peripheral nerves, joint or muscle pain, development of sensory or motor deformities were recorded. The knowledge of past history of reaction was obtained from the patients and/or previous clinical records, whenever available. The patients were asked whether they had ever experienced the symptoms

Table 1. Incidence of reactional episodes and neuritis

Group (304)	Type 1 reaction			Type 2 reaction			Neuritis		
	LL (84)	BL (49)	BB (24)	LL (84)	BL (49)	BB (24)	LL (84)	BL (49)	BB (24)
Vaccine (157)	25 (29.7%)	17 (34.6%)	6 (25.0%)	42 (50.0%)	7 (14.2%)	1 (4.1%)	31 (36.9%)	15 (30.6%)	5 (20.8%)
	48 patients (30.5%)			50 patients (31.8%)			51 patients (32.4%)		
Placebo (147)	LL (83)	BL (41)	BB (23)	LL (83)	BL (41)	BB (23)	LL (83)	BL (41)	BB (23)
	10 (12.0%)	10 (24.3%)	9 (39.1%)	43 (51.8%)	7 (17.1%)	1 (4.3%)	36 (43.3%)	12 (29.2%)	6 (26.1%)
	29 patients (19.7%) $P = 0.0413$*			51 patients (34.6%) $P = 0.686$			54 patients (36.7%) $P = 0.510$		
P value	0.009	0.406	0.468	0.937	0.943	0.489	0.487	0.926	0.936

*The *P* values were calculated using chi-square. The value for type 1 reaction for all categories combined ($P = 0.0413$), after Bonferroni's correction becomes $P = 0.124$. The significance for the same figures calculated by Mantel–Haenszel chi-square test is $P = 0.137$. Power size calculation for BB type is 70% for type 1 reactions.

(characteristic of reactions/neuritis). Based on their responses/clinical records, it was deduced whether they had a previous history of reaction or not. Cases with mild reaction were managed with rest, physiotherapy and non-steroidal anti-inflammatory drugs (NSAID) for a period of 6 weeks, severe cases were managed with initial hospitalization, physiotherapy, oral steroids for a period of 12–20 weeks (along with NSAID, only if necessary, to avoid any possible gastrointestinal damage). The patients given steroids with NSAID were monitored closely.

STATISTICAL ANALYSIS

The comparative statistical analysis of reactional and neuritis episodes in the vaccine and placebo groups has been done using chi-square test. Incidence of reactions and neuritis, in cases stratified by the previous history of occurrence, has been analysed by Mantel–Haenszel test. The impact of initial BI on reaction and neuritis incidence has been analysed using chi-square test for trend. A P value of <0.05 was considered as significant.

Results

Table 1 presents the number of patients in vaccine and placebo group, under three leprosy types LL, BL and BB, experiencing type 1, type 2 reactions and neuritis. The numbers of these patients have been compared in total, as well as against the respective categories from vaccine and placebo groups. There is no statistically significant difference with respect to type 2 reactions and neuritis in any leprosy type. The incidence of type 1 reactions was higher in the vaccine group as a whole ($P = 0.041$, relative risk ratio 1.79); however, the difference did not remain significant ($P = 0.124$) on correction of P value for number of variables. The higher incidence of type 1 reaction in the vaccine group can be attributed to the higher incidence in LL leprosy, i.e. 25 patients out of 84 (29.7%) in the vaccine group, as against 10 out of 83 (12.0%) in the placebo group. This difference is statistically significant ($P = 0.009$). However, this is to be stated that nine out of 25 (36%) patients in the vaccine group and two out of 10 (20%) in the placebo group had a previous history of reaction and this difference was statistically significant ($P = 0.008$, data not shown in table).

Table 2 presents the occurrence of type 1 reaction, type 2 reaction and neuritis, with respect to single or multiple episodes in patients from the vaccine and placebo groups. It is seen that the single as well as multiple episodes of type 1 reaction occurred almost in equal percentages of patients in both groups, 62.5% in vaccine and 62.1% in placebo group for single episode, and 37.5% and 37.9%, respectively, for multiple episodes. Similarly, among the patients experiencing type 2 reaction and neuritis, no statistically significant differences were observed between the two groups during treatment and follow-up.

Table 3 shows the occurrence of neuritis and reactions in patients, taking place in association or in isolation. The number of patients remaining free from any neuritis or reactional state are nearly equal in vaccine and placebo groups, i.e. 36.9% and 36.7%, respectively. Similarly the number of patients experiencing only reactions, only neuritis and those experiencing both these, also show no statistically significant difference between the two groups.

Tables 4a and b depict the impact of previous history of reaction and neuritis, respectively, on their occurrence during treatment and post-treatment follow-up. The patients

Table 2. Incidence of reactional episodes and neuritis in terms of single or multiple episodes

Leprosy type (*n*)	Type 1 reaction (no. of patients)			Type 2 reaction (no. of patients)			Neuritis (no. of patients)		
	Total	Single episode	Multiple episodes	Total	Single episode	Multiple episodes	Total	Single episode	Multiple episodes
LL (V) (84)	25	12 (48.0%)	13 (52.0%)	42	20 (47.6%)	22 (52.4%)	31	17 (54.9%)	14 (45.1%)
BL (V) (49)	17	13 (76.5%)	4 (23.5%)	7	3 (42.8%)	4 (57.1%)	15	5 (33.3%)	10 (66.6%)
BB (V) (24)	6	5 (83.3%)	1 (16.6%)	1	1	–	5	4 (80.0%)	1 (20.0%)
Total (157)	48	30 (62.5%)	18 (37.5%)	50	24 (48.0%)	26 (52.0%)	51	26 (50.9%)	25 (49.1%)
LL (P) (83)	10	5 (50%)	5 (50%)	43	17 (39.5%)	26 (60.5%)	36	12 (33.3%)	24 (66.6%)
BL(P) (41)	10	4 (40%)	6 (60%)	7	3 (42.9%)	4 (57.1%)	12	7 (58.3%)	5 (41.7%)
BB(P) (23)	9	9	–	1	1	–	6	6	–
Total (147)	29	18 (62.1%)	11 (37.9%) $P = 0.857$	51	21 (41.2%)	30 (58.8%) $P = 0.887$	54	25 (46.3%)	29 (53.7%) $P = 0.939$

P values indicate the statistical comparison between vaccine and placebo groups for type 1, type 2 reactions and neuritis. Analysis was done by Mantel–Haenszel chi-square test.

Table 3. Incidence of reaction and neuritis occurring in isolation or in combination

Group	No.	No. Rxn/neuritis	Only reaction	Only neuritis	Both Rxn and neuritis
LL(V)	4	25 (29.7%)	28	5	26
BL(V)	49	19 (38.7%)	15	6	9
BB(V)	24	14 (58.3%)	5	4	1
TOTAL	157	58 (36.9%)	48 (30.5%)	15 (9.5%)	36 (22.9%)
LL(P)	83	23 (27.7%)	24	10	26
BL(P)	41	19 (46.3%)	10	5	7
BB(P)	23	12 (52.1%)	5	2	4
Total	147	54 (36.7%)	39 (26.5%)	17 (11.5%)	37 (25.1%)
		(P = 0.485)	(P = 0.217)	(P = 0.284)	(P = 0.323)

have been segregated into two categories, those having a previous history of neuritis or reactions before commencement of therapy and those without any such history. There were no statistically significant differences in incidence of reactions in patients in the vaccine and placebo groups, adjusting the effect of presence or absence of prior history, in any of the LL, BL or BB leprosy types (Table 4a). The intra-group comparison, however, showed a statistically significant increase in reaction incidence, among patients with previous history, in the placebo group ($P < 0.001$) as compared to those without a prior history of reaction. The similar comparison was not significant statistically in the vaccine group ($P = 0.105$).

Table 4

(a) Impact of previous history of reactions (HOR) on incidence of reactions during MDT and post-RFT follow-up

	Vaccine					Placebo					P*
Group	n	HOR(+)	Incidence	HOR(−)	Incidence	n	HOR(+)	Incidence	HOR(−)	Incidence	V vs P
LL	84	31	23 (74.1%)	53	31 (58.4%)	83	20	19 (95.0%)	63	31 (49.2%)	0.905
BL	49	12	8 (66.6%)	37	16 (43.2%)	41	14	9 (64.2%)	27	8 (29.6%)	0.437
BB	24	7	3 (42.8%)	17	3 (17.6)	23	4	3 (75.0%)	19	6 (31.5%)	0.314
Total	157	50	34 (68.0%)	107	50 (46.7%)	147	38	31 (81.6%)	109	45 (41.2%)	
					P = 0.105$					P < 0.001$	

(b) Impact of previous history of neuritis (HON) on incidence of neuritis during MDT and post-RFT follow-up

	Vaccine					Placebo					P*
Group	N	HON(+)	Incidence	HON(−)	Incidence	N	HON(+)	Incidence	HON(−)	Incidence	V vs P
LL	84	9	9 (100%)	75	22 (29.3%)	83	7	5 (71.4%)	76	31 (40.8%)	0.155
BL	49	8	6 (75.0%)	41	9 (21.9%)	41	3	2 (66.6%)	38	10 (26.3%)	0.929
BB	24	1	1 (100%)	23	4 (17.3%)	23	1	1 (100%)	22	5 (22.7%)	0.085
Total	157	18	16 (88.9%)	139	35 (25.2%)	147	11	8 (72.7%)	136	46 (33.8&)	
					P < 0.001$					P = 0.09$	

P* Intergroup statistical comparison between vaccine and placebo groups, in LL, BL and BB types, adjusting the vaccine effect for the presence or absence of history of reaction/neuritis, done by Mantel–Haenszel chi-square test.

$The intra-group comparison within the vaccine and placebo groups, for incidence of reaction or neuritis, with respect to patients with and without previous history of occurrence.

Similarly, for neuritis, the comparison between the vaccine and placebo groups with respect to neuritis incidence in those with/without a previous history of neuritis did not show any significant difference in any leprosy type (Table 4b). However, a higher incidence of neuritis was found in cases with prior history, as compared to those without such history, within the vaccine group ($P < 0.001$). This difference was not statistically significant in the placebo group ($P = 0.09$).

Table 5 describes the occurrence of neuritis and reactional episodes with respect to the time of occurrence, i.e. whether during MDT or during post-MDT follow-up. It may be noted that in cases of both type 1 and type 2 reactions, majority of episodes occurred during therapy, i.e. 93.0% in vaccine and 93.3% in the placebo group; the rest of the episodes occurred during follow-up. In the case of neuritis, about 18% of episodes occurred during follow-up in vaccine group, as against 9.69% episodes in the placebo group.

Table 6a shows the sex distribution of the patients experiencing the reactional episodes and neuritis. For type 1 reactions, while a nearly equal incidence was observed for males and females in the placebo group (19.5% and 20.8%, respectively), a disparity was observed in the vaccine group patients, where a significantly higher number of male patients developed type 1 reaction in comparison to females (34.5% versus 8.3%, $P < 0.019$). This difference was also found to be statistically significant ($P = 0.02$) when analysed with respect to previous history of occurrence of reaction as shown in Table 6b. For type 2 reactions and neuritis, no statistically significant difference was found in sex distribution, both in vaccine and placebo groups.

Table 7 shows the association of initial BI on the incidence of reaction and neuritis. In vaccine group the reactions occurred in 70.3% cases in high initial (4.1–6.0) BI, 56.1% in medium (2.1–4.0) and 38.8% in low (0.3–2.0) BI patients and this association was found to be statistically significant ($P = 0.0029$). The corresponding figures in the placebo group were also significantly associated with the initial BI ($P = 0.00024$). For neuritis, the frequencies in the vaccine group were 35.3%, 36.3% and 25.9% in the three mentioned BI ranges, while the corresponding figures in placebo group were 43.6%, 39.4% and 21.4%. While borderline statistically significant difference ($P = 0.036$) was observed for neuritis incidence in the three BI ranges, in the placebo group, the difference was not significant ($P = 0.31$) in the vaccine group.

The incidence of impairments such as anaesthesia, trophic ulcers, claw-hand and grade 3 deformities, present before therapy, and those developed during therapy and post-therapy follow-up, were not different statistically in the vaccine and placebo groups. Detailed analysis is reported elsewhere.[7]

Table 5. Incidence of neuritis and reactional episodes, in relation to timing of occurrence during MDT and post-treatment follow-up

	Type 1 reaction (no. of episodes)			Type 2 reaction (no. of episodes)			Neuritis (no. of episodes)		
Group (no. of patients)	Total	During MDT	During follow-up	Total	During MDT	During follow-up	Total	During MDT	During follow-up
Vaccine (157)	72	67 (93.0%)	5 (6.9%)	100	96 (96.0%)	4 (4.0%)	98	80 (81.6%)	18 (18.3%)
Placebo (147)	45	42 (93.3%)	3 (6.7%)	103	100 (97.0%)	3 (3.0%)	105	95 (90.4%)	10 (9.6%)

Table 6
(a) Incidence of reactional episodes and neuritis among males and females

Group (304)	Type 1 reaction (patients affected)			Type 2 reaction (patients affected)			Neuritis (patients affected)		
Vaccine (157)	Total (157)	Male (133)*	Female (24)*	Total (157)	Male (133)	Female (24)	Total (157)	Male (133)	Female (24)
	48 (30.5%)	46 (34.5%)	2 (8.3%)	50 (31.8%)	41 (30.8%)	9 (37.5%)	51 (32.4%)	46 (34.6%)	5 (20.8%)
M vs F, *P* value	$P < 0.019$			$P = 0.683$			$P = 0.277$		
Placebo (147)	Total (147)	Male (123)**	Female (24)**	Total (147)	Male (123)	Female (24)	Total (147)	Male (123)	Female (24)
	29 (19.7%)	24 (19.5%)	5 (20.8%)	51 (34.6%)	41 (33.3%)	10 (41.7%)	54 (36.7%)	43 (35.0%)	11 (45.8%)
M vs F, *P* value	$P = 0.895$			$P = 0.582$			$P = 0.436$		
Statistical comparison between vaccine and placebo groups									
P value		0.010	0.413		0.768	1.00		0.945	0.126

* Previous H/o reactions was present in 44/133 (33.1%) male and 4/24 (16.7%) female patients.
** Previous H/o reactions was present in 28/123 (22.8%) male and 10/24 (41.6%) female patients.

(b) Correlation of type 1 reaction incidence, with previous history of reaction, among males and females

	Males			Females			
Group (304)	Patients with rxn	Patients with HOR(+)	Patients having rxn (HOR+)	Patients with rxn	Patients with HOR(+)	Patients having rxn (HOR+)	*P** (M vs F)
Vaccine (157)	46/133 (34.5%)	44/133 (33.1%)	15/46 (8.3%)	2/24 (8.3%)	4/24 (16.6%)	1/2 (50%)	0.02
Placebo (147)	24/123 (19.5%)	28/123 (22.8%)	9/24 (37.5%)	5/24 (20.8%)	10/24 (41.6%)	1/5 (20%)	NS

* Statistical comparison of type 1 reaction using Mantel–Haenszel test, among males and female patients, adjusted to previous history of reaction.
NS non-significant.

Table 7. Incidence of neuritis and reactional episodes, in relation to initial bacteriological indices

Group	BI range	Total	Reaction		Neuritis		Statistical difference*
			Present	Absent	Present	Absent	
Vaccine (157)	4.1–6.0	37	26 (70.3%)	11	13 (35.3%)	24	
	2.1–4.0	66	37 (56.1%)	29	24 (36.3%)	42	$P = 0.0029$ (Reactions)
	0.3–2.0	54	21 (38.8%)	33	14 (25.9%)	40	$P = 0.31$ (Neuritis)
Placebo (147)	4.1–6.0	39	29 (74.3%)	10	17 (43.6%)	22	
	2.1–4.0	66	33 (50%)	33	26 (39.4%)	40	$P = 0.0024$ (Reactions)
	0.3–2.0	42	14 (33.3%)	28	9 (21.4%)	33	$P = 0.036$ (Neuritis)

*Statistical difference calculated by chi-square for trend test, in the three BI ranges, in the vaccine and placebo groups.

Discussion

Reversal (type 1) reactions (RR) occur frequently in borderline and subpolar LL leprosy but are relatively uncommon in polar LL types, possibly due to the LL patients' inability to mount a CMI response to the pathogen. The occurrence of reversal reaction following immunostimulation has been reported in LL leprosy by Convit *et al.*, where RR was found to be associated with lepromin conversion in indeterminate leprosy patients who were administered multiple injections of a vaccine containing heat killed *M. leprae* and BCG. The reaction was not seen if, either *M. leprae* or BCG were given alone.[8] In another study from Bombay, India, where ICRC vaccine was administered in addition to chemotherapy with DDS, five out of 46 (10.8%) LL patients developed RR.[9] However our findings should be interpreted with caution. The data would have been better analysed using a multivariate analysis. This would have permitted analysis controlling for potentially confounding factors such as history of reaction.

The preliminary results of this trial on RR published earlier (on 106 patients, 53 cases in vaccine and placebo group each) showed an overall incidence of type 1 reaction of 22.6% in vaccine and 15.1% in the placebo group and the difference was not statistically significant.[10] The current study pertains to 304 patients (157 vaccine and 147 placebo cases) who have been followed up for over 8 years where the frequency of RR was significantly higher in the vaccine group as a whole ($P = 0.041$, relative risk 1.79), mainly due to high incidence among LL patients (29.7% in vaccine versus 12% in placebo, $P = 0.009$). This has been found to be due to the higher number of patients in the vaccine group with a previous history of reaction. The corresponding difference was not statistically significant in patients with BL and BB leprosy.

The overall incidence of reversal (type 1) reactions in the present study was higher in comparison to that reported in a few other studies, e.g. 10.8% developed RR following immuno-chemotherapy with dapsone and ICRC vaccine,[7] 8.2% patients in a study from Hyderabad, Southern India[11] and 8–10% occurrence in the study by Chaudhary *et al.* from Calcutta,[12] employing MDT and low-dose Convit vaccine. This disparity could have been influenced by several factors, for example variation in anti-leprosy treatment (dapsone and

rifampicin in study with ICRC and three-drug MDT in other two studies; in fact, no immunomodulator was used in the study from Hyderabad), or a difference in sample size (55, 193, 150 and 304 patients evaluated in studies with ICRC, Hyderabad study, Calcutta study and ours, respectively). In addition, the nature of the study also has a considerable impact on recording of incidence of reactions; the study from Hyderabad was based on retrospective analysis of clinical records of the patients, while other three studies were prospective ones. Ours was an institutional study where all efforts were made to keep the chances of reactions or neuritis going unnoticed, to the minimum.

The incidence of type 2 reactions reported in the preliminary results of our study pertaining to a total of 86 cases from both groups together, was 10/45 (22.2%) in vaccine and 12/41 (29.2%) in the placebo group.[13] The trend observed in the preliminary results is maintained in the data now available, on larger number of patients, followed up for a longer duration. The overall incidence of type 2 reaction was 31.8% in the vaccine and 34.6% in the placebo group (not significantly different statistically).

Recurrence of reactional episodes (single or multiple episodes) has been reported in a study from Thailand where 77.3% patients undergoing type 2 reactions had multiple episodes and 31.4% patients having type 1 reactions had multiple episodes and this difference in occurrence of multiple episodes of type 1 and type 2 reactions was found to be statistically significant ($P < 0.001$).[14] However, we did not find any statistically significant difference between patients experiencing multiple episodes of type 1 (37.5% in vaccine group and 37.9% in placebo) or type 2 (52% in vaccine group and 58.8% in placebo) reactions. There was no significant difference between the vaccine and placebo group patients experiencing multiple episodes of type 1 and type 2 reactions and neuritis.

The occurrence of reactions and neuritis may take place either together or in isolation. In retrospective analysis of reversal reactions in the study from Hyderabad, 19 patients out of 43.1% had skin lesions only, 31.8% only neuritis and 22.7% had both skin lesions and neuritis.[11] The corresponding figures in our study are comparable with these (Table 3). This observation highlights once again the importance of meticulous clinical examination with special efforts to look for inflamed nerves, which otherwise might be overlooked in the absence of inflamed skin lesions.

The disproportionately higher incidence of type 1 reaction noticed among females in the study from Thailand by Scollard *et al.*[14] seems to have been reversed in our study where great preponderance of affected male subjects was noticed (34.5% versus 8.3%, $P = 0.019$) in the vaccine group. One might speculate that this higher incidence in males could be due to the higher number of male patients with a previous history of reactions in comparison to female patients. However, the analysis for the reaction incidence adjusting with the previous history of reaction the statistical difference was done and the difference was statistically significant ($P = 0.02$; Table 6b). The number of female patients in this study as such is very small to draw any concrete conclusion. The corresponding difference was not significant statistically in the placebo group. For type 2 reactions and neuritis, the differences in incidence among males and females were not statistically significant.

The initial BI seems to have a considerable influence on the incidence of reactional states, though the incidence of neuritis does not seem to be affected by it to the similar extent. This is demonstrated by higher frequency of reactions occurring in cases with high initial BI (4.1–6.0), and lower frequencies in the medium (2.1–4.0) and low (0.3–2.0) BI patients (Table 7). Unlike reactions, the statistical difference for neuritis in the different BI categories was non-significant ($P = 0.31$) in the vaccine group and borderline significant ($P = 0.036$) in the

placebo group; the latter does not remain significant on correction applied for the number of variables tested. In our study a great majority of reactional episodes (nearly 93% in both groups) occurred during MDT when the patients were bacteriologically positive. Very few (6–7%) episodes occurred during post-treatment follow-up, when the patients were bacteriologically negative. This could be due to traces (debris) of the mycobacteria, which may not have been cleared completely and could stimulate the immune system. The picture was similar in both vaccine and placebo groups, the plausible explanation could be that MDT was continued in both the groups till the point of slit-skin smear negativity, resulting in marked reduction in incidence of reactional states during follow-up. The incidence of neuritis and reactions was higher in those patients having a previous history of occurrence. This once again stresses the need for more careful monitoring to detect the reactional states and neuritis at the outset among the cases with a previous history of reactions and neuritis.

To conclude, the comparative assessment of incidence of type 2 reaction and neuritis, in the vaccine and placebo group patients, demonstrates no major differences. The incidence of type 1 reaction is higher in the vaccine group in the LL type, but this is also due to significantly higher number of patients having a previous history of occurrence. The more important point to be stressed is that it does not lead to any corresponding rise in impairments or deformity. Therefore it may be inferred that the addition of Mw vaccine to standard MDT does not lead to any appreciable rise in any untoward outcome with respect to neuritis or reactional states, over and above that observed with MDT alone.

Acknowledgements

The trials were supported by Department of Biotechnology, Ministry of Science and Technology, Government of India. The authors wish to express their gratitude to Dr Padam Singh, Director, Institute for Research in Medical Statistics (ICMR), New Delhi, for his able guidance and Dr Abha Aggarwal (ICMR) for her hard work in carrying out the statistical analysis of the data. The paramedical and technical assistance of Mr Anil Bobbin, Mr Dinesh Negi and Mr Amarnath Prasad are gratefully acknowledged. Above all, the authors feel immensely indebted to the patients of this study, without whose support and cooperation, such a long study would not have been possible.

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