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Reversal reaction in multibacillary leprosy patients following MDT with and without immunotherapy with a candidate for an antileprosy vaccine, *Mycobacterium w*

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Summary Immunotherapy with a candidate for an antileprosy vaccine, *Mycobacterium w*, was given in addition to standard multidrug therapy (MDT) to 53 multibacillary lepromin negative patients belonging to BB, BL and LL types of leprosy (vaccine group). An equal control group received MDT and injections of micronized starch as placebo. Both the vaccine and placebo were administered intradermally every 3 months. The patients were evaluated at determined intervals by clinical, bacteriological and histopathological parameters and lepromin testing. Reactional episodes were analysed with reference to incidence, onset, frequency and severity during and after release from treatment (RFT). Incidence of reversal reaction (RR) was marginally higher in the vaccine group (22·6% vaccine group *vs* 15% control group). All cases with a history of downgrading type 1 reaction developed RR during therapy. Most episodes occurred within the 1st year of the commencement of therapy—50% developing within 3 months. Late reversal reaction (after RFT) were observed in 3·8% of cases in both groups, and 50% of the reactors in the control group and 33% in the vaccine group had repeated reactional episodes. Incidence of neuritis associated with RR as well as isolated neuritis was similar in both groups.

Introduction

This study forms part of a large-scale immunotherapeutic clinical trial of a candidate for an antileprosy vaccine, *Mycobacterium w* (*M.w*), which is currently in progress at the Dr. RML and the Safdarjang Hospitals of New Delhi in association with the National

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Institute of Immunology and the Institute of Pathology (Indian Council of Medical Research), New Delhi. Multibacillary leprosy patients receiving immunotherapy with *M.w* along with MDT have shown a distinctly better clinical improvement and a more rapid bacterial clearance than those who received MDT alone.[1,2] There was lepromin conversion in all BB, 85% BL and more than 80% LL patients after 8 doses of vaccine, but in only 40% BB and 0% BL and LL patients under MDT alone.[2] In the vaccine group, the percentage of BL and LL cases becoming clinically and bacteriologically inactive after 24 pulses was 100% and 66·6%, respectively, whereas in the control group it was only 50% and 15%, respectively.[2] Histopathologically, 75% LL cases and 85% BL cases receiving MDT and vaccine either showed upgrading along the spectrum or a clearance of granuloma from the dermis, in comparison with 50% BL and 33·3% LL cases in the control group.[3]

In this paper we have analysed the data of 106 cases who have completed 2 years of therapy with special reference to the incidence, onset, frequency and severity of reversal reaction (RR) observed during therapy and after RFT.

Materials and methods

SUBJECTS AND DESIGN

Phase II/III immunotherapeutic trials with *M.w* were started in January 1987. Patients reporting to the Urban Leprosy Centres of 2 hospitals in Delhi were screened by clinical, immunological, bacteriological and histopathological criteria. Patients with no previous history of antileprosy treatment (a) falling in the BB, BL and LL spectrum of the disease (according to the Ridley–Jopling Scale); (b) showing the presence of bacilli in slit skin smears; (c) having lepromin A (armadillo derived) negativity initially and (d) having features of BB, BL and LL type of disease histopathologically were inducted into the study. Standard MDT as recommended by NLEP of India[4] was given to all those enrolled. In addition, half of the patients received *M.w* vaccine and the other half received an injection of micronized starch as placebo. The allotment of the patients was done in a randomized manner according to a code supplied to the attending physician. Random testing of urine for the presence of dapsone was carried out in all patients before their induction to this study in order to confirm that they had not recently received treatment with dapsone.[5]

The trials were single blind, in which the Head of the Department of Dermatology, Venereology and Leprology knew the group to which each patient belonged, whereas the patients and the attending physicians, as well as the investigators carrying out the histopathology, BI and clinical scores, did not know whether the patient was receiving the vaccine or placebo. In all, 106 patients participated in this study and are either taking or have had regular treatment for at least 24 months.

Vaccine—dosage, administration and regimen

The vaccine was injected intradermally in the deltoid region. A total of 8 vaccine doses were given at 3 monthly intervals. The first dose was 1×10^9 autoclaved bacilli in 0·1 ml physiological saline (0·85% NaCl). Subsequent doses contained 5×10^8 killed bacilli.

Placebo

This consisted of 1 g micronized starch (Sarabhai Chemicals, Baroda, India), dissolved in 100 ml of distilled water and autoclaved. Dosage, administration and regimen was similar to that of the vaccine.

Lepromin

Armadillo lepromin containing 4×10^7 killed bacilli per ml, supplied by WHO, was used for the study.

Multidrug therapy (MDT)

This consisted of 2 weeks of intensive therapy with 600 mg rifampicin, 100 mg clofazimine and 100 mg of dapsone daily. Subsequently, the patients received for 2 years the WHO recommended regimen of 600 mg of rifampicin and 300 mg clofazimine once a month supervised plus 100 mg dapsone and 50 mg clofazimine daily, self-administered. Drug regularity was checked by randomly conducting a spot test for DDS in the urine[5] and by counting the tablets.

EVALUATION

General

Patients were evaluated clinically by Ramu's clinical score[6,7] at 6 monthly intervals. Bacterial indices (BIs) were calculated at 3 monthly intervals according to Ridley's logarithmic scale.[8] A 0·1 ml dose of lepromin A (armadillo derived) was injected every 3 months. An induration of more than 3 mm diameter was taken as positive. Histopathological examination of a typical skin lesion was done every 6 months.

For Reaction

A proforma sheet for leprosy reaction was filled in at the time of the patient's induction and subsequently during each reactional episode. The present and past history of reaction, detailed clinical findings (with special reference to exaggeration of existing skin lesions), appearance of fresh lesions and their density and distribution were noted. The presence or absence of constitutional symptoms like a rise in temperature, malaise, insomnia, anorexia, pain/tenderness of peripheral nerves, recent development of sensory and motor deformities, joint and muscle pain, eye changes, testicular tenderness and swelling, lymph nodes, spleen and liver enlargement were carefully recorded. The grading of the RR and the treatment administered was also documented. RR was graded as mild or severe.[9] Mild reactions 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 12–20 weeks) along with NSAID whenever necessary.

The diagnosis of reaction was made clinically. In doubtful cases skin biopsy was carried out to confirm the clinical diagnosis. Lepromin testing was done during each episode of RR.

Table 1. Number of cases enrolled in study

Type of leprosy	MDT + vaccine (vaccine group)	MDT + control (control group)	Total
BB	14	14	28
BL	14	14	28
LL	25	25	50
Total	53	53	106

Table 2. Incidence of type 1 reactions previous to therapy

Group	DG* type 1 reaction	Isolated neuritis
Vaccine	3/53 (2-BL, 1-BB)	2/53 (1-BB, 1-LLs)
Control	3/53 (2-BL, 1-BB)	2/53 (2-BL)

Figures in parentheses indicate break up according to type of leprosy.
* DG = downgrading.

Table 3. Incidence of reversal reaction (RR) during therapy

Group	Number of cases					
	Reversal reaction			Isolated neuritis		
Vaccine	BB	BL	LL	BB	BL	LL
	4/14	5/14	3/25	1	0	1
	Total 12/53 (22·6%)					
Control	BB	BL	LL	BB	BL	LL
	4/14	3/14	1/25	0	1	0
	Total 8/53 (15·1%)					

Results

Table 1 gives the number of patients belonging to different types of leprosy who were inducted into the study, i.e. 106, with the vaccine and control group each containing 50%.

Table 2 describes the incidence of type 1 reactions and isolated neuritis observed before or at the time of the patients' enrolment in this study—3 cases had downgrading type 1 reaction and 2 cases had a history of isolated neuritis in each group.

Table 3 depicts the incidence of RR and isolated neuritis observed during the 2 years of therapy in both vaccine and control groups according to the spectrum of leprosy.

Table 4. Time of onset of reversal reactions after initiating therapy

Group	No. of patients with RR	Time of onset of RR (months)				
		0–3	3–6	6–12	12–24 or >24	After RFT (late reversal reaction)
Vaccine	12	5	2	4	—	1+(1*)
Control	8	4	1	2	—	1+(1*)

A patient from the vaccine group and 1 from the control group had had previous episode of RR while under MDT.

Table 5. Frequency of reversal reactions

Group	No. of patients	No. of patients showing		
		1 episode	2 episodes	>2 episodes
Vaccine	12	8 (66·6)*	4 (33·3)	—
Control	8	4 (50)	2 (25)	2 (25)

* Numbers in parentheses are percentages.

Table 6. Severity of reversal reactions

Group	No. of episodes	Mild	Severe
Vaccine	16	9 (56·3)*	7 (43·7)
Control	15	10 (66·6)	5 (33·3)

* Numbers in parentheses are percentages.

In the vaccine group 22·6% of cases developed RR in comparison to 15·1% in the control group during the 2-year follow-up period. This difference is not statistically significant (proportion test, $z = 0{\cdot}993$). In the BB group incidence of RR was the same (28·6%) in both groups whereas among both BL and LL patients, this was 20·5% in the vaccine group and 10·2% in the control group. This difference is not statistically significant (proportion test, $z = 1{\cdot}255$). All cases with a history of downgrading reaction in both groups developed RR after therapy.

We observed 2 cases of isolated neuritis in the vaccine group (1 BB case with left ulnar nerve and 1 LL case with right ulnar nerve involvement). These 2 cases had a previous history of ulnar neuritis. In the control group, out of the 2 BL cases with a previous history of neuritis, only 1 developed ulnar neuritis.

As is evident in Table 4, the onset of all reversal reactions were seen within 1 year of the initiation of therapy in both groups, 50% developing reactional episodes within 3 months

irrespective of the type of leprosy—4 patients (3 within 6 months and 1 after 22 months of RFT) had late reversal reactions. All 4 patients at the time of late RR had negative BI, higher positivity of lepromin reaction and histopathologically non-specific infiltration, i.e. a mild to moderate degree of lymphocytic infiltration in the dermis.

In the control group, 50% of the cases with RR had 2 or more reactional episodes, whereas only 33% of cases with RR in the vaccine group had multiple episodes of reaction (Table 5).

A marginally higher percentage of severe type of reactional episodes were observed in the vaccine group compared to the control group (43·7% *vs.* 33·3%) (Table 6). However, this difference was not statistically significant ($z = 0{\cdot}595$).

In both groups (except 1 BB and 1 BL case in the control group) patients with RR had lepromin conversion either before or at the time of reaction. In the control group, lepromin conversion was transiently observed at the time of RR and subsequently there was a reversion to negativity.

Discussion

Reversal reactions commonly occur in borderline leprosy patients and are associated with an abrupt rise in cell mediated immune responses to mycobacterial antigens.[10] They are most frequently seen during the initial phases of the introduction of chemotherapy.[10] But this reaction is rarely observed among LL patients, possibly due to their inability to mount CMI responses to this pathogen.

Following immunostimulation, a rise in the incidence of RR even in the LL group is easy to predict. It has been reported in 3 out of 4 LL patients given multiple injections of Transfer Factor by Hastings & Job.[11] Convit *et al.*[12] observed a reversal reaction associated with lepromin conversion in indeterminate leprosy cases who had been administered multiple injections of a vaccine containing heat killed *M. leprae* and BCG. The reaction was not seen if either *M. leprae* and BCG were given alone. In another study from Bombay, India, where killed ICRC bacilli was administered in addition to chemotherapy with DDS, 5 out of 96 LL cases developed reversal reaction.[13]

In our study an equal percentage of BB patients in the vaccine and control groups developed reversal reaction but among BL and LL patients a higher incidence of RR was observed in the vaccine as against the control group (20·4% *vs.* 10·2%). An interesting observation among the LL vaccinated patients was that 3 of them had RR episodes. These 3 cases were highly bacilliferous (BI 6+, 5+ and 4+). After the 1st dose of vaccine two of them developed mild RR during the 3rd month of therapy) with minimal BI fall. The 3rd patient presented with a reactional episode at the 9th month with a BI fall from 5·8+ to 3·5+. All of them demonstrated lepromin conversion. Therefore, in full agreement with Bhatki *et al.*,[13] there appears to be little relationship between bacillary load and occurrence of RR. This is also supported by the observation that more than half of the cases developing RR had the onset of reaction within the first 3 months of treatment initiation, despite minimal BI fall during this period.

Higher incidence of RR in the vaccine group could be due to a rapid stimulation of cell-mediated immunity. This would explain the slightly higher incidence of a severe form of RR in the vaccine group. But once the reaction is controlled with steroids, the relapse of reaction is less frequent among vaccinated patients. This may probably be due to a steady

and gradual build up of cell-mediated immunity with subsequent vaccination. Immunochemotherapy with *M.w* along with chemotherapy possibly results in a rapid clearance of mycobacterial antigens and establishes a delicate balance between antigens available for immune reactions and host responses.

The major problem associated with RR is that of neurological complications leading to deformities. In our series, 4 out of 16 episodes of RR in the vaccine group and 3 out of 15 episodes in the control group had neuritis (right lateral popliteal nerve leading to foot drop (1), left facial nerve with resultant facial paralysis (1), unilateral ulnar neuritis (3), bilateral ulnar neuritis with claw hand (1) and unilateral ulnar neuritis with claw hand (1). All patients with neuritis were managed with oral steroids, physiotherapy and the affected part of the anatomy was rested. This resulted in complete motor recovery in all but 1 case (in the vaccine group). This patient underwent reconstructive surgery for claw hand after RFT. Isolated neuritis was observed in 2 cases in the vaccine group and 1 case in the control group.

Thus, the vaccine did not precipitate any additional neurological complication—an important observation in the context of introducing an immunomodulator. This clinical finding was corroborated by the histological observation that after vaccination, no damage or increased intra- or perineurial lymphocytic infiltration was seen in dermal nerve twigs.[3]

In conclusion, it appears that *M.w*, the candidate for an antileprosy vaccine can be safely used as an adjunct to existing MDT, a finding based on its ability to cause rapid clinical and bacteriological improvement and histological upgrading.

References

[1] Talwar GP, Zaheer SA, Mukherjee R, Walia R, Misra RS, Sharma AK, Kar HK, Mukherjee A, Parida SK, Suresh NR, Nair SK, Pandey RM. Immunotherapeutic effects of a vaccine based on a saprophytic cultivable mycobacterium, *Mycobacterium w*, in multibacillary leprosy patients. *Vaccine*, 1990; **8:** 121–9.

[2] Talwar GP, Zaheer SA, Suresh NR, Parida SK, Mukherjee R, Singh IG, Sharma AK, Kar HK, Misra RS, Mukherjee A. Immunotherapeutic trials with a candidate anti-leprosy vaccine based on *Mycobacterium w*. *Trop Med Parasitol*, 1990; **41:** 369–70.

[3] Mukherjee A, Zaheer SA, Sharma AK, Misra RS, Kar HK, Mukherjee R, Talwar GP. Histopathological monitoring of immunotherapeutic trials. *Int J Lepr*, 1992; **60:** in press.

[4] Indian Association of Leprologists (IAL). Consensus on treatment regimens in leprosy and the problems of drug delivery. *Ind J Lepr*, 1984; **56:** 158–9.

[5] Naik SS, Sahasrabudhe RV. Comparative study of different drug compliance tests available in leprosy. *Ind J Lepr*, 1988; **60:** 270–6.

[6] Ramu G, Desikan KV. A follow up study of borderline tuberculoid leprosy under sulphone monotherapy. *Ind J Lepr*, 1988; **60:** 26–33.

[7] Iyer CGS, Balakrishnan S, Ramu G. A comparison of low and conventional dosages of dapsone in the treatment of lepromatous leprosy in India. *Lepr Ind*, 1977; **49:** 372–88.

[8] Ridley DS, Hilson GRF. A logarithmic index of bacilli. *Int J Lepr*, 1967; **35:** 184–6.

[9] Waters MFR. Treatment of reaction in leprosy. *Lepr Rev*, 1974; **46:** 337.

[10] Waters MFR, Rose P. Reversal reaction in leprosy and their management. Editorial. *Lepr Rev*, 1991; **62:** 113–21.

[11] Hastings RC, Job CK. Reversal reaction in lepromatous leprosy following transfer factor therapy. *Am J Trop Med Hyg*, 1978; **27:** 1004.

[12] Convit J, Ulrich M, Aranzazu N. Vaccination in leprosy—observations and interpretations. *Int J Lepr*, 1980; **48:** 62–5.

[13] Bhatki WS, Chulawala RG, Bapat CV, Deo MG. Reversal reaction in lepromatous patients induced by a vaccine containing killed ICRC bacilli—A report of five cases. *Int J Lepr*, 1983; **51:** 466–72.

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Poussées réactionnelles chez les lépruex multibacillaires a MDT avec ou sans immunothérapie par *Mycobacterium w*, un eventuel vaccin contre la lèpre

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Résumé En plus de la thérapeutique multidrogue standard (MDT), 53 lépreux multibacillaires, négatifs à la lépromine et appartenant aux types de lèpre BB, BL et LL (groupes de vaccination) ont reçu une immunothérapie avec un bacille qui pourrait éventuellement devenir un vaccin contre la lèpre, *Mycobacterium w*. Un groupe de témoins en nombre égal a reçu MDT et des injections d'amidon micronisé comme placebo. Le vaccin, comme le placebo, était administré en injection intradermique tous les 3 mois. Les paramètres cliniques, bactériologiques et histopathologiques et le test à la lépromine étaient évalués à intervalles déterminés chez les malades. On a noté, pour chaque épisode de réaction l'incidence, le début, la fréquence et la sévérité pendant et après la cessation du traitement (RTF). L'incidence des réactions lépreuses (RR) a été légèrement plus élevée dans le groupe vacciné (22,6% dans le groupe vacciné contre 15% dans le groupe témoin). Tous les cas présentant une histoire de réaction de déclin type 1 ont présenté une poussée réactionnelle pendant le traitement. Le plus grand nombre des épisodes s'est produit au cours de la première année de traitement, dont 50% dans les premiers 3 mois. Des réactions lépreuses tardives (après RTF) ont été observées dans 3,8% des cas dans les deux groupes, et 50% des malades réagissant dans le groupe témoin et 33% dans le groupe vacciné ont eu des épisodes réactionnels répétés. L'incidence des névrites associées à RR, comme celle des névrites isolées, a été similaire dans les deux groupes.

Reacción invertida en los pacientes leprosos multibacilares después de tratamiento multidroga con y sin inmunoterapia y una posible vacuna antileprosa, *Mycobacterium w*

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Resumen Se administró una posible vacuna antileprosa, *Mycobacterium w*, en conjunto con una terapia multidroga (MDT) normal, a 53 pacientes multibacilares lepromin-negativos, de los tipos BB, BL y LL de lepra (el grupo vacunado). Un grupo de control de igual magnitud recibió MDT e inyecciones de almidón micronizado como placebo. Se administró la vacuna y el placebo por vía intradérmica cada 3 meses. Se controlaron los pacientes a intervalos regulares mediante parámetros clínicos, bacteriológicos e histopatológicos, y pruebas de lepromin. Se analizaron casos de reacción con referencia a incidencia, comienzo, frecuencia y severidad, durante y después de darles de alta del tratamiento (RFT). La incidencia de reacción invertida (RR) era levemente superior en el grupo vacunado (22,6% para el grupo vacunado comparado con 15% del grupo de control). Todos los casos con antecedentes de una reacción Tipo 1 de degradación desarrollaron RR durante la terapia. La mayoría de casos ocurrieron en menos de 1 año del comienzo de la terapia, 50% de ellos en menos de 3 meses. Se observó reacción invertida retardada (después de RFT) en un 3,8% de casos en ambos grupos, y un 50% de los reactores en el grupo de control y 33% del grupo vacunado tuvieron incidentes de reacción repetidos. La incidencia de neuritis asociada con RR, además de neuritis aislada, era similar en ambos grupos.