INTERNATIONAL JOURNAL OF LEPROSY

Volume 73, Number 2
Printed in the U.S.A.
(ISSN 0148-916X)

Comparative Evaluation of Immunotherapeutic Efficacy of BCG and *Mw* Vaccines in Patients of Borderline Lepromatous and Lepromatous Leprosy[1]

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ABSTRACT

Background. Even after 12 months of multi-drug therapy (M.D.T.) multibacillary (MB) therapy patients with high bacterial index (B.I.) continue to harbor dead bacilli and viable persisters, which lead to immunological complications such as recurrent reactions and late relapses, respectively. To achieve faster killing of viable bacilli and clearance of dead bacilli, various immunotherapeutic agents (vaccines and cytokines) are being evaluated as an adjunct to M.D.T.

Aims and objectives. To evaluate the role of BCG and *Mw* vaccines in the immunotherapy of leprosy.

Materials and methods. Sixty untreated leprosy patients with a BI = 2 were randomly allocated to three treatment groups of twenty patients each. Group A patients received World Health Organization (W.H.O.) (12 months M.D.T.-MBR) and BCG intradermally (10^5 live bacilli /per dose). Group B patients were administered 12 months M.D.T.-MBR and *Mycobacterium w* (1×10^8) killed bacilli as first dose and 0.5×10^8 /dose in subsequent doses. Group C received 12 months M.D.T. MBR with 0.1 ml of normal saline as placebo. All the groups received 4 doses of vaccine or normal saline repeated at three monthly intervals. The patients were periodically monitored by clinical (Ramu's score), bacteriological (slit skin smear), and histopathological (skin biopsy) parameters, six monthly during and one year after completion of M.D.T.

Results. The mean reduction in clinical scores in BCG and *Mw* groups was significantly more when compared to controls. At 12 and 24 months, the patients in BCG group had significantly greater reduction in Ramu's score as compared to those in the *Mw* group. BI declined by 2.40 units/year in patients receiving BCG, 2.05 units/year in the *Mw* group and 0.85 units/year in the control group. Although the incidence of type 1 reactions was apparently more in the BCG and *Mw* vaccinated groups, the incidence of type 2 reactions, neuritis and development of new deformities was less as compared to the controls.

Conclusions. In our study, BCG exhibited slightly better and faster effect on bacteriological clearance and clinical improvement as compared to *Mw* vaccine in borderline lepromatous (BL)/ polar lepromatous (LL) patients with a high initial B.I., however, their effect on histopathological (decrease in GF) improvement was comparable. Both the vaccines were well tolerated. Immunotherapy can be a useful adjunct to the shortened (12 months) M.D.T. MB regimen to decrease the risk of reactions and relapses in highly bacilliferous BL/LL patients.

RESUME

Contexte. Même après 12 mois de polychimiothérapie (PCT), des patients multibacillaires (MB) avec index bactérioscopique (IB) élevés continuent à avoir des bacilles morts ou des bacilles viables et persistants, qui mènent fréquemment à des complications immunologiques comme des réactions récurrentes ou des rechutes tardives, respectivement. Afin d'atteindre une éradication plus rapide des bacilles viables et une élimination plus rapide des bacilles morts, des agents immuno-thérapeutiques variés (vaccins et cytokines) sont en cours d'évaluation, comme compléments à la PCT.

[1] Received for publication on 15 June 2004. Accepted for publication on 1 October 2004.

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Buts et objectifs. Evaluer le rôle des vaccins BCG et *Mw* dans l'immunothérapie de la lèpre.

Matériels et méthodes. Soixante patients hanséniens encore non-traités, avec IB de 2, furent attribués en aveugle à 3 groupes de traitements de 20 patients chacuns. Le groupe A reçut la PCT pour patients MB de 12 mois recommandée par l'OMS et une injection intradermique de BCG (10^5 bacilles vivants par dose). Au groupe B fut administré 12 mois de PCT-MB et *Mycobacterium w* (1×10^8 bacilles morts en primo-injection et $0{,}5 \times 10^8$ en injections de rappel). Le groupe C reçut PCT-MB pendant 12 mois et 0,1 ml de liquide physiologique comme placebo. Tous les groupes ont reçu, tous le 3 mois, 4 doses de vaccins ou bien du liquide physiologique normal. Un suivi clinique (score de Ramu), bactériologiques (test du suc dermique) et histopathologiques (biopsies cutanées) des patients fut effectué tous les 6 mois pendant le traitement puis 1 an après la fin du traitement par la PCT.

Résultats. La réduction moyenne des scores cliniques des groupes traités au BCG ou à *Mw* fut significativement plus importante que celui du groupe contrôle. A 12 et 24 mois, les patients du groupe BCG avaient une réduction plus importante du score de Ramu que le groupe *Mw*. L'IB a diminué de 2,40 unités par an chez les patients ayant reçu le BCG, 2,05 unités par an dans le groupe *Mw* et de 0,85 unités/an dans le groupe contrôle. Bien que l'incidence des réactions de type 1 fût apparemment plus élevée dans les groupes vaccinés au BCG et *Mw*, l'incidence des réactions de type 2, les névrites et le développement de nouvelles déformations a été moindre chez les vaccinés que chez les contrôles.

Conclusions. Dans cette étude, le BCG a démontré un effet plus rapide et plus important en terme de clairance bactériologique et d'amélioration des signes cliniques que le vaccin *Mw* chez les patients lépromateux borderline (BL) ou les patients lépromateux polarisés (LL) avec un IB initial élevé. Cependant leurs effets sur l'aspect microscopique (diminution de la fraction granulomateuse GF) restaient très comparables. Les 2 vaccins furent tous deux fort bien tolérés. L'immunothérapie peut être très utile comme traitement complémentaire à la PCT-MB abrégée à 12 mois, pour diminuer le risque de réactions et de rechute(s) parmi les patients BL/LL fortement infectés par les bacilles de Hansen.

RESUMEN

Panorama. Los pacientes multibacilares (MB) con índices bacterianos (BI) altos siguen teniendo bacilos muertos y bacilos viables persistentes aún después de 12 meses de tratamiento con PQT, lo que conduce a complicaciones inmunológicas tales como reacciones recurrentes y recaídas tardías, respectivamente. Para acelerar la muerte de los bacilos vivos y la eliminación de los bacilos muertos se están evaluando varias vacunas y citocinas como agentes inmunoterapéuticos.

Metas y objetivos. Evaluar el papel de las vacunas BCG y *Mw* en la inmunoterapia de la lepra.

Materiales y Métodos. Sesenta pacientes con lepra sin tratamiento y con un BI = 2, se asignaron, al azar, a 3 grupos de tratamiento de 20 pacientes cada uno. El grupo A recibió la PQT de la OMS para lepra MB por 12 meses y BCG intradérmicamente (10^5 bacilos vivos por dosis). El grupo B recibió la PQT de la OMS para lepra MB y *Mw* ($1{\times}10^8$ bacilos muertos como primera dosis y 0.5×10^8 en las dosis subsecuentes). El grupo C recibió 12 meses de PQT-OMS-MB y 0.1 ml de solución salina como placebo. Todos los grupos recibieron 4 dosis de vacuna o de salina a intervalos de 3 meses. Los pacientes fueron evaluados periódicamente usando parámetros clínicos (escala de Ramu), bacteriológicos (examen de linfa cutánea) e histopatológicos (en biopsia de piel).

Resultados. Los grupos tratados con BCG y con *Mw* evolucionaron mejor que los pacientes del grupo control. Dentro de los pacientes vacunados, los del grupo BCG mostraron una reducción en la escala de Ramu significativamente mayor que los pacientes del grupo *Mw*. El BI mostró una disminución de 2.4 unidades/año en los pacientes con BCG, de 2.05 unidades/ año en el grupo *Mw*, y de 0.85 unidades/año en el grupo control. Aunque la incidencia de reacciones tipo I fue aparentemente mayor en los grupos vacunados con BCG y *Mw*, la incidencia de reacciones tipo 2, neuritis y nuevas deformidades, fue menor que la observada en el grupo control.

Conclusión. En nuestro estudio, el grupo vacunado con BCG mostró una mejor y más rápida evolución clínica y bacteriológica que el grupo vacunado con *Mw*, y esto ocurrió tanto en los pacientes BL como en los pacientes LL con altos BI; sin embargo, la mejoría histopatológica (disminución en la fracción granuloma) fue comparable en ambos grupos. Ambas vacunas fueron bien toleradas. La inmunoterapia puede ser un complemento útil a la PQT-MB de duración acortada (12 meses) para reducir el riesgo de reacciones y recaídas en los pacientes BL/LL altamente bacilíferos.

Leprosy continues to be a public health problem in seventeen endemic countries of the world. Since the inception of M.D.T. in 1982, there has been 85% reduction in global prevalence of leprosy. The prevalence of leprosy in India has fallen from 57 per 10,000 in 1981 to 3.3 per 10,000 in 2003 ([5]), but India still accounts for 78% of all the leprosy cases in the world, and its elimination program is of major importance for global leprosy control.

The duration of M.D.T. regimen for MB leprosy was reduced to 12 months by the W.H.O. Expert Committee on Leprosy in 1997 ([34]); however, information regarding efficacy and safety of shortened MB regimen (12 months) is very limited at present. There are reports of relapses in MB patients treated with fixed duration treatment (FDT) from some centers, especially in patients with higher B.I. ([6, 11, 21, 32]). Patients in the lower spectrum, i.e., BL/LL leprosy, have partial or complete lack of CMI, which is responsible for persistence of dead as well as live bacilli even after adequate therapy. A variety of possible factors which have been postulated for deficient cell mediated immunity are: genetic constitution, primary fault in T-cells and macrophages, inappropriate suppressor cell activity, and abnormal antigen presentation ([26]). In these cases the dead bacilli and their antigens and viable persisters lead to immunological complications such as recurrent reactions and late relapses, respectively. To achieve faster killing of bacilli and clearance of dead bacilli as well as possible alteration of immunological unresponsiveness in these patients, immunotherapy in the form of vaccines and cytokines has been tried.

Antigens of various mycobacteria have been observed to cross-sensitize the immune response to *M. leprae* and this might help in augmenting CMI in leprosy. Prominent among these are BCG ([16]), BCG plus killed *M. leprae* ([7]), *Mycobacterium w (Mw)* ([9, 14, 15, 16, 23]), and Indian Cancer Research Center (ICRC) bacillus ([3]). Many studies have confirmed the immunotherapeutic efficacy of *Mw* vaccine, but very few have evaluated the efficacy of BCG or compared BCG and *Mw* vaccines. Katoch, *et al*. ([16]) compared the immunotherapeutic efficacy of BCG and *Mw* vaccines in MB patients and found both to be effective however; patients were given M.D.T. until smear negativity in their study. Present study, was designed to compare the immunotherapeutic efficacy of BCG and *Mw* vaccines in BL/LL leprosy patients treated with fixed duration (12 months) W.H.O. M.D.T. MBR.

MATERIALS AND METHODS

Sixty untreated bacteriologically positive multibacillary leprosy patients (BL, LL) with a B.I. ≥ 2, age more than 12 years, attending the Leprosy Clinic of Post Graduate Institute of Medical Education and Research, Chandigarh, India were randomly allocated in 3 groups of twenty patients each.

All patients received W.H.O. M.D.T. (MBR) for one year. In addition, the first group (group A) was given BCG vaccine (0.1 ml/dose, containing 10^5 viable units of BCG; (BCG vaccine laboratory, Guindy, Chennai, India). Group B received *Mw* vaccine (1×10^8 killed bacilli in the first dose and 0.5×10^8/dose in the subsequent doses), and group C was administered normal saline 0.1 ml intradermally as control. The patients in groups A, B, and C received four doses of BCG, *Mw* vaccine and normal saline, respectively, at three month intervals. Informed consent was taken from all the patients before inducting them into the study. Patients who were pregnant, in type 1 lepra reaction, and those who had any immunodeficiency disorder or were taking immunosuppressive therapy, were excluded from the study.

Patients were classified according to the Ridley-Jopling classification ([10]) and diagnosis in all patients was confirmed by histopathology. During and after M.D.T. treatment, activity of the disease was routinely assessed clinically by Ramu's clinical scoring system ([12]) (minimum score = 0 and maximum = 28). A detailed history including symptoms and occurrence of reactions and findings on physical examination were recorded for all the patients, initially monthly for one year and every 3 months later on. Type 1 reaction (reversal reaction) was diagnosed on noting visible changes in the existing lesions in the form of erythema, swelling (edema), presence of subjective feeling of warmth, tingling sensations and or local tenderness, or appearance of new lesions, associated with or without constitutional symptoms. Type 2 reaction was diag-

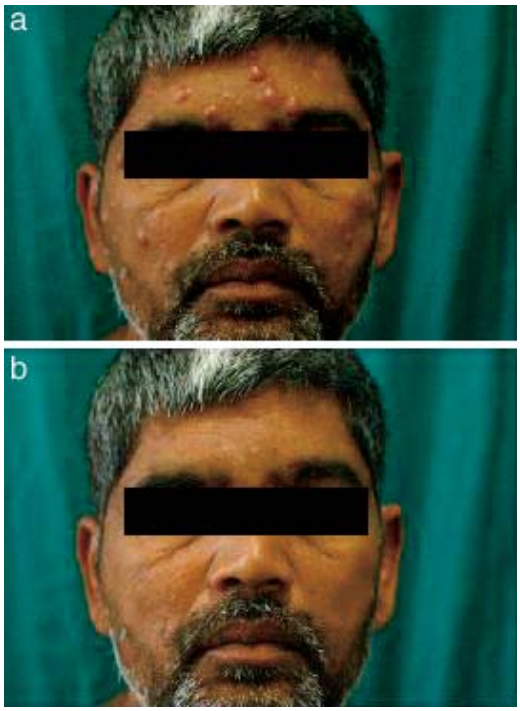

FIG. 1(a). Pre-treatment—histoid leprosy with multiple shiny erythematous nodules in Group A (BCG).

FIG. 1(b). Post-treatment—same patient at 12 months, almost complete resolution of the lesions.

nosed on the basis of presence of constitutional symptoms of varying degree like fever, aches, joint pains, bony tenderness with characteristic evanescent lesions of erythema nodosum leprosum (ENL) associated with or without specific organ involvement like eye, testis, kidney, etc. Only neuritis was diagnosed by the presence of persistent and demonstrable tenderness in the nerves (thickened or not) in the absence of any evidence of inflammation in the leprosy lesions but with nerve function impairment. Tenderness of nerves in the presence of inflamed skin lesions of type 1 or type 2 reaction was considered to be part of the reaction. Patients with deformities were classified according to W.H.O. grading of 1998([34]).

Slit-skin smears were taken initially, and then every 6 months from the same sites. Skin biopsy was also repeated from the same site after 6, 12, and 24 months of starting treatment for histopathologic evaluation. The biopsies were graded as LL, BL, borderline (BB), or borderline tuberculoid (BT) based on the characteristic distribution of various types of inflammatory cells as well as the character, location, and extent of granuloma. Biopsy was classified as non-specific infiltrate (NSI) if there was no evidence of a granuloma, absence of acid-fast bacilli (AFB) and presence of minimal and scattered peri-appendageal lympho-histiocytic infiltrate in different parts of dermis. The results were also compared in respect to clearance of dermal granuloma(s) by measuring the estimated reduction in granuloma fraction (GF) (i.e., fraction of dermis occupied by the granuloma(s) and clearance of acid-fast bacilli) ([8]).

All the patients were followed up for two years. The data was analyzed and the therapeutic efficacy of the vaccines compared using the paired "*t*" test.

RESULTS

The mean age of the patients in all the groups was similar. Maximum number of patients were in the age range of 18 to 40 years. A majority of the patients in all the groups were males (46/60, 76%). Group A had 8 (40%) LL, 10(50%) BL, and 2 (10%) patients of histoid leprosy. In group B there were 10 (50%) LL, 9 (45%) BL, and 1 patient with histoid leprosy. Group C had 12 (60%) LL, and 8 (40%) BL patients. The clinical scores, B.I., and GF were analyzed and it was observed that the patients in the three groups were almost comparable by all these parameters.

All the patients exhibited reduction in clinical scores with therapy. The mean reduction in clinical scores in both groups A and B was significantly more at 6 and 12 months when compared to group C ($p < 0.05$). At 24 months the patients in group A still had significantly greater reduction in clinical score but the difference between groups B and C was not statistically significant (Figs. 1a and 1b). The difference between groups A and B was not significant at 6 months, but at 12 and 24 months the patients in group A had significantly greater reduction in the score as compared to group B ($p < 0.05$). (Table 1).

The fall in B.I. was significantly more in groups A and B ($p < 0.01$) at 6, 12, and 24 months when compared to group C. On comparing the BCG and *Mw* groups the mean decrease in B.I. was more in the BCG

FIG. 2(a). Pre-treatment LL patient in BCG group —diffuse granulomatous infiltration in dermis. GF = 80%. (H&E × 55).

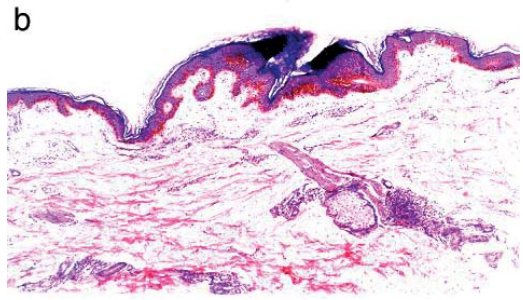

FIG. 2(b). Post-treatment (same patient at 12 months) —almost complete clearance of granulomas. GF = 5%. (H&E × 55).

group ($p < 0.01$) at 12 and 24 months (Table 2). At the end of two years, 14 (70%) patients in group A were smear negative as compared to 13 (65%) in group B and 6 (30%) in group C. Almost all the patients showed a rapid decline in morphological index (M.I.) during treatment. None of the patients showed solid staining bacilli at the end of 12 months.

All the patients showed reduction in GF but it was more marked in group A when compared to group C at 12 months ($p < 0.05$) (Table 3). In relation to the reduction in GF, the difference between the groups B and C, as well as the groups A and B, was not significant ($p > 0.05$) at any time during the study (Figs. 2a and 2b).

Histological upgrading from LL to BL was seen in 8/12 (66.6%) patients in the BCG group, 7/11 (63.6%) patients in *Mw* group and 5/12 (41.6%) patients in the control group. Upgrading from BL to BT disease was seen only in the vaccine treated groups. These changes were seen in 1/10 (10%) patient in BCG group and 3/9 (33.3%) patients in *Mw* group. At 24 months, near complete clearance of granulomas and AFB with histological picture suggestive of non-specific infiltrate was seen in 17 (85%) patients in the BCG group, 12 (60%) in the *Mw* group, and 6 (30%) in the control group.

A majority of patients in each group had experienced one or more episodes of reaction before starting antileprosy treatment. However, only those reactions which occurred in the previous two years (frequency and degree of severity was also noted) were considered for comparison in post-treatment statistical evaluation. History of type 1 reactions was present in 4 (20%) patients in group A, and 3 (15%) patients each in groups B and C. During the course of study, the number of patients who experienced type 1 reaction were 6 (30%), 6 (30%), and 4 (20%) in groups A, B, and C, respectively. There was an apparent but not statistically significant increase in the incidence of type 1 reactions in groups A and B, as compared to group C. However, majority of these reactions were mild and were managed with anti-inflammatory drugs (NSAIDS).

During the period of study, there was a significant decrease in the incidence of type 2 reactions in group A ($p < 0.05$). The inci-

TABLE 1. *Clinical scores (mean ± S.D.) before and after treatment.*

	Baseline	At 6 months		At 12 months		At 24 months	
		Score	Reduction	Score	Reduction	Score	Reduction
A	16.55 ± 3.60	11.90 ± 2.42	4.65 ± 2.05	8.30 ± 2.70	8.25 ± 2.63	4.60 ± 1.84	11.95 ± 3.20
B	15.50 ± 3.7	11.8 ± 2.78	3.70 ± 1.92	10.05 ± 2.68	5.45 ± 2.58	6.65 ± 1.66	8.85 ± 2.94
C	16.20 ± 5.06	14.65 ± 4.92	1.55 ± 1.19	12.60 ± 4.75	3.60 ± 1.46	8.45 ± 2.52	7.75 ± 3.09

TABLE 2. *Bacteriological index (mean ± S.D.) before, during and after treatment.*

	Baseline	At 6 months		At 12 months		At 24 months	
		Score	Reduction	Score	Reduction	Score	Reduction
A	4.00 ± 0.85	2.35 ± 1.08	1.65 ± 1.18	1.60 ± 0.91	2.40 ± 1.12	0.10 ± 0.30	3.90 ± 0.91
B	3.80 ± 0.95	2.45 ± 1.25	1.35 ± 0.93	1.75 ± 1.29	2.05 ± 1.09	1.00 ± 1.07	2.80 ± 1.00
C	3.50 ± 1.05	3.20 ± 0.95	0.30 ± 0.47	2.65 ± 0.87	0.85 ± 0.67	1.70 ± 0.97	1.80 ± 0.89

dence of type 2 reaction decreased in all the groups after starting therapy; the decrease was from 45% (pre-treatment) to 15% (post-treatment) in group A and from 45% to 20% in group B, whereas in Group C there was hardly any change, from 40% to 35%, and 4 (20%) of the patients in group C continued to have recurrent episodes throughout the study period. The decrease in the incidence of type 2 reactions in groups B and C was not statistically significant.

At the beginning of the study, positive history of neuritis was present in 8 (40%), 7 (35%), and 9 (45%) patients in groups A, B, and C, respectively. After starting treatment, the incidence of neuritis decreased in all the patients. In group A, 2 (10%); group B, 3 (15%); and in group C, 6 (30%) patients experienced neuritis as part of reactions. However, the decrease in the incidence of neuritis was statistically significant only in group A. All the patients with neuritis were managed with systemic steroids, NSAIDS and rest.

Grade 2 deformities like claw hand, foot drop, and trophic ulcers were present in 4 (20%) patients in group A and 5 (25%) each in groups B and C. None of the patients in groups A and B developed any new deformities nor was there any further deterioration in the deformity status, whereas in group C, 3 (15%) patients developed new deformities during the study period, (claw hand = 2 and foot drop = 1).

All the patients in group A developed an erythematous papule at the site of BCG vaccination, which progressed to shallow ulcer and healed spontaneously with scarring. Three patients in this group developed secondary infection of the ulcer with associated regional lymphadenopathy and required a course of antibiotics. Similarly, in the *Mw* group as well, all the patients developed erythema and induration or an inflammatory papule at the injection site, and in 15 (75%) of these patients ulceration occurred which healed spontaneously within 3 to 4 weeks. No systemic complications were noted following vaccination with BCG or *Mw.*

All patients tolerated M.D.T. well except for the occurrence of dapsone syndrome in three patients (2 in group A and 1 in group B), who recovered completely following withdrawal of dapsone.

DISCUSSION

Multidrug therapy (M.D.T.) has been a very successful development in the treatment of leprosy. However, most of the patients in the lepromatous spectrum were still harboring dead bacilli at the end of two years of treatment with M.D.T., indicating their poor ability to clear the bacilli. Immunotherapy with vaccines, drugs and cytokines could be useful in these patients in the very specific role of augmenting the CMI leading to faster killing of *M. leprae* and clearance of dead bacilli, thereby reducing the risk of relapse and reactions.

There are many reports in the literature, which show that the immunological unresponsiveness to bacillary antigens of *M. leprae,* in multibacillary patients (BL, LL) may be altered by various immunological approaches ([3, 7, 9, 13, 14, 15, 16, 22, 23]). Although the precise mechanism of action of these vaccines is yet unknown, certain assumptions can be put forward based on the above studies and results of other clinical trials. *Mw* and BCG vaccines are able to override the immunological non-responsiveness to bacillary antigens in multibacillary patients by generation of cross-reactive Th_1 type of clones and amplification of IFN-γ production with a concomitant decrease in levels of TNF-α and IL-10.

In our study, the reduction in the clinical scores was significantly more marked in the BCG and *Mw* treated groups as compared to controls (M.D.T. alone) at 6 and 12 months ($p < 0.05$), however, BCG resulted

TABLE 3. *Granuloma fraction (GF) (mean ± S.D.) at baseline and after treatment.*

	Baseline	At 6 months		At 12 months		At 24 months	
		Score	Reduction	Score	Reduction	Score	Reduction
A	55.75 ± 21.04	32.00 ± 18.52	23.75 ± 10.37	10.25 ± 10.81	45.50 ± 16.05	2.00 ± 3.40	53.75 ± 19.18
B	55.00 ± 22.47	29.00 ± 0.04	26.00 ± 13.43	13.75 ± 12.55	41.25 ± 16.69	3.00 ± 4.97	52.00 ± 21.11
C	55.25 ± 23.92	35.00 ± 7.91	20.25 ± 11.41	22.75 ± 14.09	32.50 ± 14.18	10.75 ± 11.15	44.50 ± 19.66

in greater reduction in the clinical scores as compared to the *Mw* at 12 and 24 months ($p < 0.01$). All the previous studies on *Mw* vaccine have also reported significant clinical improvement due to faster clearance of bacilli ([9, 14, 15, 30, 33, 35]).

The average decline in B.I. with M.D.T. has been reported to be 0.57 to 1.01 units/year ([1]). In our study, bacterial indices declined by 2.40 units/year in patients receiving BCG, 2.05 units/year in *Mw* group, and 0.85 units/year in the control group, the fall becoming more apparent in immunotherapy groups at 6, 12, and 24 months. The decline in B.I. was significantly more in the BCG treated group when compared to *Mw* treated group. The differences between BCG and *Mw* vaccine groups observed by us are not in consonance with the observations made by Katoch, *et al*. ([16]) who found the fall in B.I. to be significantly more in the *Mw*-treated group at 12, 18, and 24 months ($p < 0.05$) as compared to the BCG group.

Faster reduction in bacterial load and changes in the cellular composition of the granuloma(s) from lower to higher spectrum and reduction in the granuloma fraction, observed in all of our patients in groups A and B reflects the upgrading of CMI following vaccination. Similar histological/immunological upgrading has also been reported in all previous studies ([9, 14, 15, 30, 33, 35]). Katoch, *et al*. ([16]) showed better histological improvement and immunological upgrading with *Mw* vaccine when compared to BCG, but in our study the difference between the two vaccine groups was not statistically significant for these parameters.

Leprosy reactions have a great significance in the course of the disease. Although the incidence of ENL appears to have fallen with the introduction of M.D.T., still a majority of patients with high smear positivity are tormented by recurrent episodes of ENL ([17, 25]). The incidence of type 2 reactions decreased in all our patients after starting therapy but it was more in the BCG treated group. Reduction in the incidence of type 2 reactions following immunotherapy has been observed in other studies as well. ([9, 16, 25, 27, 30, 33]).

Incidence of reversal reactions in MB patients treated with M.D.T. alone is reported to vary from 9% to 41% in hospitalized patients ([20, 25]). In majority of the earlier studies and as observed by us although there is an apparent increase in the incidence of reversal reactions in patients treated with *Mw* /BCG vaccines as compared to the group given M.D.T. alone, it did not achieve statistical significance ([9, 14, 15, 16, 27, 28]).

During the follow-up, it was reassuring to note that there was a lower incidence of neuritis in the vaccine treated groups [BCG = 2(10%); *Mw* = 3(15%)] as compared to the figure of 30% for the control group. This is in concurrence with an earlier study by Talwar, *et al*. ([30]) where the control group had significantly more episodes of neuritis compared to the vaccine group. However, the decrease in the incidence of neuritis was statistically significant only in the BCG group.

A steady fall in the deformity rate among new cases has been observed following the introduction of M.D.T. since 1980 ([4, 28]), but patients can have further deterioration of their existing deformities during treatment and thereafter due to increased incidence of reactions and neuritis ([28]). In our study none of the patients in the vaccine treated groups developed any new deformity or deterioration of the pre-existing deformity, but in the control group 3 (15%) patients developed grade 2 deformities. Similar observations have been made after immunotherapy with *Mw* vaccine by Sharma, *et al*. ([28]) and with BCG + killed *M. leprae* by Convit, *et al*. ([7]).

The vaccines were well tolerated and only local complications like ulceration and

mild secondary infection were seen. No systemic complications developed following administration of either of the vaccines. Development of ulceration and scarring which were hardly of any consequence have also been reported in earlier studies [9, 15, 16, 23, 30, 33]. Three patients developed dapsone syndrome, which is certainly a very high incidence for dapsone hypersensitivity. This was probably a chance occurrence, however such an observation of rising incidence of dapsone hypersensitivity in the last two decades has been made by workers from other parts of India [18, 24]. Dapsone was stopped in all these patients, they were given the vaccines as per schedule and none of them developed any other complications.

Ours is the only study after Katoch, *et al*. [16] where BCG and *Mw* have been compared. In the study by Katoch, *et al*. [16], M.D.T. and vaccines (at 6 month intervals) were administered until the patients attained smear negativity whereas in our study all the patients received M.D.T. (MBR) for one year and 4 doses of vaccines at intervals of 3 months.

We observed that BCG combined with M.D.T. produced better bacteriological clearance, faster clinical improvement as well as significant reduction in the incidence of neuritis and type 2 reactions than *Mw,* although both the vaccines were almost comparable in the histological upgrading. Katoch, *et al*. [16] reported better histological upgrading and bacteriological clearance with *Mw*. It is difficult to decide as to which biological parameters should be given more significance (bacteriological or histopathological) in evaluating the immunotherapeutic efficacy of a vaccine. Histopathological improvement seems to follow bacillary clearance but they can occur simultaneously and are inter-related but may not exactly follow each other. Immunological investigations like lepromin test, serology, cytokine assays and lymphocyte transformation tests as well as bacillary ATP measurement, macrophage based assays or DNA/RNA probes which directly measure the immunological upgrading and killing of viable bacteria, respectively, may provide a better answer to some of these questions; however, the results have not always been unequivocal.

Although no exact cause can be attributed to the observed better efficacy of BCG vaccine in our study, the following hypothesis can be proposed: different immunostimulatory response of BCG in different groups of people similar to the wide range of its prophylactic efficacy in different trials (20% to 80%) [2, 29], shorter interval between the doses, and the fact that BCG contains live attenuated bacilli (whereas *Mw* contains killed bacilli) hence they multiply and stay for longer period in the patient and may continue to augment the immunostimulatory/immunomodulatory action of BCG vaccine. These hypotheses can only be confirmed by studying these vaccines in large number of patients who are followed up for longer periods and by using a combination of better investigative immunological tools as stated above.

At present, based on the results of our study and the previous similar studies on BCG and *Mw* vaccines, we can conclude that both these can prove to be important immuno-therapeutic tools in the management of BL/LL patients with high smear positivity. In the present scenario of decentralization of leprosy services, reduction in the duration of MB treatment to 12 months, with no strict slit skin smear monitoring and absence of rather essential long term follow-up, BCG appears to be a better option than *Mw* because it is cheap and easily available.

Problems in field implementation may be patient selection; as SSS is not being done so B.I. cannot be used as a criterion. Studies have shown that number of lesions/ thickened nerves or extent of disease (number of body areas involved) may be used to predict smear positivity [19, 31]. Based on these criteria bacilliferous multibacillary (BL/LL) patients can be offered benefits of immunotherapy. Other problem that needs to be addressed is, training of health workers in diagnosing and identifying patients with multibacillary disease. As far as the supply and administration of vaccine is concerned, BCG vaccine is freely available in all the health centers in India (supplied under Universal immunization program of Government of India), and the health workers are well trained to administer the vaccine so there should not be any operational difficulty to add BCG vaccine to our ongoing National Leprosy Elimination Program (NLEP).

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