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Pilot study to determine acceptability and ability of heat-killed *Mycobacterium leprae* plus BCG (HKML+BCG) vaccine to induce skin test conversion

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Summary Although local reactions, including erythema, induration and ulcers, appeared in every patient after the injection of the combined HKML+BCG vaccine, they were accepted by the patients. There was no tendency for the local reaction to become aggravated after repeated vaccination. However, systemic reactions, mainly iridocyclitis and complaint of numbness of the fingers and toes, became quite common after the 5th vaccination and therefore significantly reduced the acceptability of vaccine by injection. It seems that repeated vaccination might activate the iridocyclitis, but the relationship between the complaint of numbness and vaccination has not been well established. Neither typical ENL nor reversal reaction had been observed throughout the trial.

A significant proportion of patients converted to SMLA positivity after repeated vaccination. However, it seems the positive status was not stable as many of them reverted to negative after the following vaccination. After the 7th vaccination, the positive conversion rate to SMLA-I was 45% and to SMLA-II was 35%. After the 8th vaccination, 66·7% of patients converted to Mitsuda reaction positive, which has been confirmed by histopathological examination. Nevertheless, further follow-up is required in order to determine whether or not such conversion will be of a long duration.

The reactions to SMLA-I and SMLA-II were associated but only correlated at a moderate level. Overall, the positive conversion rate to SMLA-I was significantly higher than that to SMLA-II after repeated vaccination. Neither the early reaction nor the late (Mitsuda) reaction of the lepromin test were correlated to either SMLA reaction.

The repeated vaccination of HKML+BCG vaccine did not affect the weakly-positive anti-PGL-1 *Mycobacterium leprae* antibody level seen in the skin-smear negative lepromatous patients participating in this study.

Introduction

Immunotherapy represents a potential approach of stimulating specific cell-mediated immune responsiveness to *Mycobacterium leprae*, which is lacking in patients with

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multibacillary leprosy, especially near the lepromatous pole. If successful, immunotherapy might accelerate the removal of persisting viable organisms, thereby reducing the rate of relapse after stopping chemotherapy, and facilitate clearance of the dead organisms, thus reducing the frequency and severity of ENL. To date, only a limited amount of information is available on potential immunotherapeutic treatment. Convit and his colleagues have claimed the therapeutic efficacy of a vaccine consisting of heat-killed *M. leprae* (HKML) plus BCG.[1]

The objectives of the project are: 1, to assess the acceptability to the patients of repeated vaccination with the combined (HKML + BCG) vaccine as a first step to independently evaluate its therapeutic effects; and 2, to assess the efficacy of the (HKML + BCG) vaccine in terms of conversion of the negative response to soluble *M. leprae* skin test antigen (SMLA) and Mitsuda lepromin among skin smear-negative lepromatous patients.

Materials and Methods

PATIENTS

A total of 30 leprosy patients, 23 male and 7 female, with an age range from 32 to 63 years, were selected for the trial. All of them had been diagnosed, confirmed by histopathology, as BL or LL leprosy with Mitsuda reaction negative (<3 mm), and treated with chemotherapy at least 5 years before the trial; the initial BI was at least 3+ or more according to the Ridley–Jopling scale but the patients had become skin smear-negative with no active lesions after effective chemotherapy, and showed no response (0 mm) to both types (Rees and Convit) of SMLAs in skin-test during the preliminary screening of the trial. Before the first vaccination 22 out of the 30 cases were PPD (RT 23, 2 TU/0·1 ml) positive. Antileprosy chemotherapy was continued during the trial.

SKIN TEST ANTIGENS AND VACCINES

In order to avoid the batch-to-batch variation in potency, the same batches of antigens/vaccines including both types (Rees and Convit) of SMLA, PPD (RT 23, 2 TU/0·1 ml, Copenhagen), Mitsuda lepromin, HKML (armadillo-derived, 3×10^9 AFB/ml, IMMLEP *M. leprae* Bank, London) and lyophilized BCG (Institut Pasteur, Paris) were used throughout the trial. They were obtained through the arrangement of the THELEP Steering Committee, WHO.

SKIN-TESTS, BLOOD SAMPLE COLLECTIONS AND VACCINATIONS

According to the protocol, all the patients received (HKML + BCG) vaccine every 3 months for a total of 8 vaccinations. The patients were skin-tested with both SMLAs 3 days before each vaccination. PPD was tested as well, as long as the induration in response to PPD was 9 mm or less. A blood sample was collected for PGL-1 antibody assay at the time of each skin testing. Both SMLA and PPD were injected strictly intradermally in a volume of 0·1 ml each, and each new injection was given 2 cm distal to the previous one. The results were read 72 hr after the injections. The reading of the skin-

testing was made 'blindly' by 2 independent assessors and the results were communicated independently to a 3rd person.

If both results were similar (within 1 mm) the results were recorded; if the 2 results differed by more than 1 mm, the assessors re-read the skin reactions independently until they reached the same result. Each vaccine dose, in a total volume of 0·3 ml, consisted of 6×10^8 AFB of HKML and 0·2 mg of BCG to those patients with induration of 9 mm or less in response to PPD, or 0·02 mg of BCG to those with induration of 10 mm or more in response to PPD. Each dose was injected strictly intradermally, and divided equally in 3 different sites (deltoid areas). At the end of the trial, i.e. after the 8th vaccination, the patients were administered a skin test with Mitsuda lepromin, and the early reaction (72 h after the injection) and late or Mitsuda reaction (4 weeks after the injection) to lepromin were measured, and in some cases biopsy was taken from the site where Mitsuda reaction was thought to be positive.

M. LEPRAE ANTIBODY ASSAY

As mentioned above, blood samples were collected at the time of each skin test and the sera was preserved in a deep freezer ($-75°C$). The ELISA technique was used to measure the IgM and IgG antibodies against the conjugate of natural trisaccharide component of PGL-1 of *M. leprae* and bovine serum albumin (BSA) (NT-O-BSA).

MONITORING FOR SIDE-EFFECTS AND ACCEPTABILITY TO THE VACCINATION

During the course of the trial, patients were interviewed and examined regularly and frequently for side-effects, including local and systemic adverse reactions, and acceptability to the vaccination. In fact, since all these patients were hospitalized due to various reasons for the duration of the trial, such interviews and examinations were very convenient. The patients had the right to refuse to continue the vaccination and skin-testing if they felt that the reaction, either local or systemic, was unacceptable.

Results

ACCEPTABILITY TO THE PATIENTS OF REPEATED VACCINATION WITH HKML + BCG

Local reactions

Various degrees of local reaction occurred even after the first vaccination. Usually from day 2 after vaccination, patients felt itching at the site of injection together with erythema and induration of a diameter of 10 mm or more, and 7 to 10 days later, in every patient an ulcer appeared near the centre of the induration. During the following month, the ulcer produced a scab, followed by reformation of an ulcer. In some patients, this cycle was repeated several times. In most cases, it took 45–60 days before the ulcer was healed. Occasionally, ulcers might continue until the next vaccination. The diameters of the ulcers ranged from 3 to 7 mm. As shown in Table 1, there was no tendency for the ulcers to become larger and the length of ulceration did not last longer during the course of

Table 1. The diameters (mm) of vaccination ulcers

Vaccination							
1st	2nd	3rd	4th	5th	6th	7th	8th
5·1 ± 1·1 (n = 30)	4·4 ± 0·8 (n = 30)	4·4 ± 0·7 (n = 30)	4·3 ± 0·7 (n = 29)	4·2 ± 0·6 (n = 22)	4·1 ± 0·4 (n = 14)	4·0 ± 0·4 (n = 21)	4·0 ± 0·4 (n = 21)

repeated vaccination. In general, the local reactions were accepted by the patients and none of them refused the vaccination because of local reactions.

Systemic reactions

Up to the first 3 vaccinations, no definite systemic reaction had been observed. However, after the 4th vaccination, 2 patients had a fever, of approximately 38°C, together with a painful swelling of the axillary lymph node. After the 5th vaccination, 8 patients (26·6%) developed iridocyclitis and 5 patients (16·6%) complained of numbness of the fingers and toes but without significant positive signs. The patients who developed iridocyclitis did not have any other signs of leprosy reaction and all of them had similar episodes before vaccination. It is likely that repeated vaccinations might activate the iridocyclitis. Numbness of the fingers and toes (apart from the hypertrophy of cervical vertebra) was confirmed by X-ray examination in 1 patient. In the other 4 patients these symptoms could not definitely be attributed to vaccination despite the fact that the complaint gradually disappeared within 6 months after stopping the vaccinations. Because of these adverse reactions, only 14 patients (46·6%) received the 6th vaccination. The acceptance rate, as shown in Figure 1, was increased somewhat at the 7th and 8th vaccination after palliative treatment was given. Because of systemic reactions only 12 patients (40%) had completed the 8 vaccinations and another 7 (23·3%) had accepted 7 vaccinations. However, neither typical ENL nor reversal reaction had been observed throughout the trial.

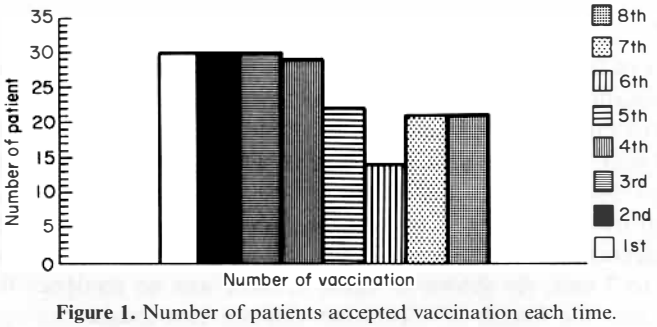

Figure 1. Number of patients accepted vaccination each time.

Table 2. SMLA Skin-test reactions (mm) before and after each vaccination

Case no.	Before		First		Second		Third		Fourth		Fifth		Sixth		Seventh	
	I*	II†	I	II	I	II	I	II	I	II	I	II	I	II	I	II
1	0	0	7	0	10	0	10	0	12	0	0	0	7	7	7	7
2	0	0	0	0	5	0	15	8	0	0	0	0	0	0	3	0
3	0	0	0	0	0	0	10	10	12	12	10	7	12	8	12	10
4	0	0	0	0	0	0	5	5	7	0	0	0	2	5	ND	ND
5	0	0	0	0	0	0	0	0	0	0	0	0	4	2	5	5
6	0	0	0	0	3	3	0	0	7	0	0	0	3	0	7	5
7	0	0	0	0	0	0	0	0	0	0	0	0	7	4	5	4
8	0	0	5	6	13	15	13	15	14	12	10	15	14	12	15	12
9	0	0	0	0	10	5	10	5	12	0	6	8	8	6	7	4
10	0	0	0	0	10	5	3	3	0	5	0	0	12	10	16	12
11	0	0	0	0	0	0	10	8	ND	ND	ND	ND	0	0	7	3
12	0	0	0	0	0	0	0	0	0	10	ND	ND	12	8	12	8
13	0	0	0	0	20	17	14	12	ND	ND	ND	ND	ND	ND	ND	ND
14	0	0	0	0	0	0	0	0	12	13	ND	ND	6	6	ND	ND
15	0	0	0	0	0	8	3	7	10	8	8	7	15	10	10	10
16	0	0	0	0	13	10	10	8	10	8	ND	ND	ND	ND	ND	ND
17	0	0	12	13	15	15	13	14	11	10	ND	ND	ND	ND	ND	ND
18	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND
19	0	0	0	0	0	0	8	0	5	0	ND	ND	4	4	10	8
20	0	0	0	0	8	8	6	6	ND	ND	ND	ND	ND	ND	ND	ND
21	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
22	0	0	0	0	0	0	0	6	0	0	ND	ND	6	0	0	0
23	0	0	0	0	6	7	12	14	8	8	ND	ND	6	7	10	8
24	0	0	0	0	0	0	8	6	ND	ND	ND	ND	10	8	ND	ND
25	0	0	0	0	0	5	10	12	ND	ND	ND	ND	ND	ND	ND	ND
26	0	0	0	0	8	5	8	9	0	0	7	5	9	8	8	10
27	0	0	0	0	5	3	0	0	11	8	8	4	10	8	10	8
28	0	0	0	0	0	0	6	8	2	2	ND	ND	0	0	8	8
29	0	0	0	0	10	10	12	12	ND	ND	ND	ND	10	10	8	11
30	0	0	0	0	0	0	6	6	5	0	ND	ND	12	10	12	10
Positivity‡ rate (%)																
	0		3·3		26·7		41·4		40·9		15·4		39·1		45·0	
		0		3·3		16·7		24·1		22·7		7·7		21·7		35·0

* Rees antigen.
† Convit antigen.
‡ Induration ⩾ 10 mm.

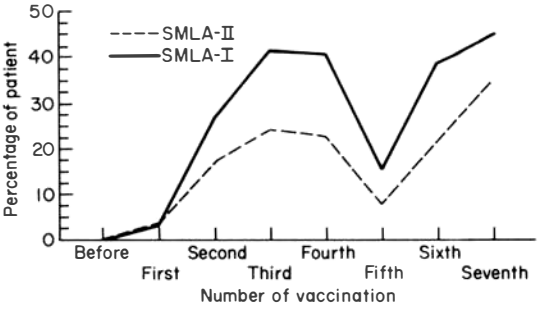

Figure 2. Positive conversion rates to both SMLAs.

SKIN-TEST CONVERSION TO PPD AND SMLAS

PPD test

There were 22 patients who were PPD-positive before the 1st vaccination. Among the 8 patients who were PPD-negative at the beginning of the trial, 3 converted to positive after the 1st vaccination, 4 converted after the 2nd vaccination, and the 8th remained PPD-negative after the 3rd, also his last, vaccination.

SMLA tests

As mentioned above, 2 types of SMLA were used. SMLA-I refers to Rees antigen and SMLA-II refers to Convit antigen. A significant proportion of the patients converted to a positive reaction after repeated vaccinations, 45% to SMLA-I and 35% to SMLA-II after the 7th vaccination. In fact, conversion to SMLA occurred in a certain proportion of patients after the 2nd vaccination. As shown in Table 2 and Figure 2, the conversion rates had reached the plateau after the 3rd vaccination. Although the conversion rates to both antigens had significantly reduced after the 5th vaccination, i.e. immediately before the 6th vaccination, this was probably due to the fact that 9 out of the 16 patients who had refused the 6th vaccination and SMLA tests were positive already to at least one SMLA antigen either after the 3rd or the 4th vaccination. A total of 21 (70%) patients were converted to SMLA-positive at least once to at least one antigen during the course of the trial: 7 (Case Nos 1, 2, 9, 11, 19, 24 and 27) became positive only to SMLA-I antigen; 1 (Case No. 6) became positive to SMLA-II; and 13 (Case Nos 3, 8, 10, 12, 13, 14, 15, 16, 17, 23, 25, 29 and 30) were positive to both antigens. However, many of them reverted to negative during the following tests. For instance, among the 20 patients who received skin tests after the 7th vaccination, 13 (Case Nos 1, 2, 3, 8, 9, 10, 11, 12, 15, 23, 27, 29 and 30) had been converted to SMLA-positive to at least a minimum of one antigen after the previous vaccinations, and 7 (Case Nos 1, 2, 9, 11, 12, 23 and 29) became negative again after the 7th vaccination. Therefore, it seems that the positive status to SMLA was not stable. Table 3 presents the pooled data from all the SMLA skin test result after vaccinations. Although the responses to SMLA-I and to SMLA-II were not independent ($\chi^2 = 62{\cdot}67$, $p < 0{\cdot}001$), the correlation between them, as measured by the ϕ coefficient,[2] was only 0·63, indicating that the correlation was only moderate. In fact, the pooled data

Table 3. Association between skin test reactions to SMLA-I and SMLA-II

		SMLA-I		
		+	−	Total
SMLA-II	+	28	3	31
	−	22	114	136
Total		50	117	167

$\chi^2 = 62{\cdot}67$, $p < 0{\cdot}001$.

Table 4. SMLA skin-test reactions (mm) after the seventh vaccination and Early and Late (Mitsuda) lepromin reactions (mm) after the eighth vaccination

Case no.	SMLA-test reaction		Lepromin reaction	
	SMLA-I	SMLA-II	Early reaction	Mitsuda reaction
1	7	7	0	0
2	3	0	0	0
3	12	10	3·5	3·5
4*	ND	ND	0	5·5
5	5	5	0	0
6*	7	5	0	5
7	5	4	0	0
8	15	12	5	0
9*	7	4	4·5	5·5
10*	16	12	4	7·5
11	7	3	8	0
12	12	8	12·5	5
15	10	10	0	5·5
19	10	8	0	6·5
22	0	0	7·5	5
23	10	8	0	7
26	8	10	9·5	6·5
27	10	8	11·5	3·5
28	8	8	4	6
29	8	11	7	0
30	12	10	5·5	4
Positivity† rate (%)				
	45·0	35·0	9·5	66·7

* Biopsy was taken from the site of Mitsuda reaction.

† Induration ⩾ 10 mm for SMLA and early reaction of lepromin, and nodule ⩾ 3 mm for Mitsuda reaction.

also indicated that the positive rate (29·9%) to SMLA-I was significantly higher than the positive rate (18·6%) to SMLA-II ($p < 0{\cdot}05$).

Skin test conversion to lepromin after the 8th vaccination

Lepromin was tested in 21 patients after the 8th vaccination and the results of early and late (Mitsuda) reactions are presented in Table 4, together with their reactions to both

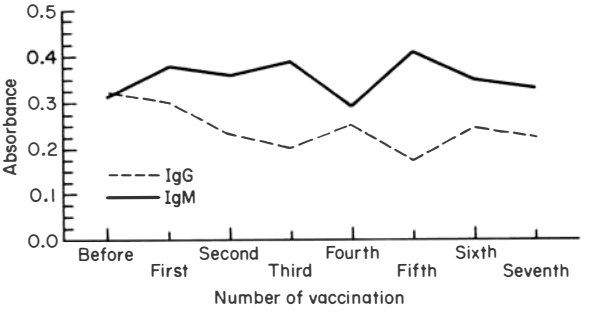

Figure 3. Levels of *M. leprae* antibody before and during vaccination.

SMLA antigens after the 7th vaccination. Only 2 (9·5%) patients were early reaction positive to lepromin, whereas 14 (66·7%) were Mitsuda reaction positive. Calculated by Fisher's exact test, the p value was 0·19 between early reaction versus SMLA-I reaction, 0·41 between early reaction versus SMLA-II reaction, 0·054 between Mitsuda reaction versus SMLA-I reaction and 0·35 between Mitsuda reaction versus SMLA-II reaction. Therefore, neither the early reaction nor the Mitsuda reaction of lepromin test were correlated to either SMLA-I or SMLA-II reaction.

Skin biopsy was taken for histopathological examination from the lepromin injected site of 4 patients (Case Nos 4, 6, 9 and 10) who showed positive Mitsuda reaction. Dr K. V. Desikan of the Leprosy Histopathological Centre, Mahatma Gandhi Institute of Medical Science, Wardha, India 'blindly' examined the biopsy slides, and all the histopathological findings were consistent with positive Mitsuda reaction.

The profile of anti-PGL-1 M. leprae *antibody during vaccination*

In our laboratory, the normal range, in terms of absorbance (A490), of IgM and IgG antibody against NT-O-BSA among non-leprosy contacts is $\leqslant 0{\cdot}28$ and $\leqslant 0{\cdot}15$, respectively. As shown in Figure 3, despite the fact that all the patients were skin-smear negative after effective treatment, the mean absorbance of their IgM and IgG antibody was slightly higher than normal values before vaccination. Since the profile remained basically the same throughout the whole period of the trial, it seems that the repeated vaccinations of (HKML+BCG) vaccine did not stimulate anti-PGL-1 *M. leprae* antibody production over the 2-year interval.

Discussion

Today leprosy is believed to be a cell-mediated immune deficiency disease. Even if multibacillary leprosy is cured following a routine treatment with any of the different effective antileprotic drugs, this deficiency is not repaired—the lepromin test is continuously negative, and some viable bacilli still exist in the host, but stopping the chemotherapy might lead to relapse of the disease, and the antigen which dead bacilli release might induce an immune reaction that is harmful to the host.

Early in the 1950s Schujman reported that after vaccination with BCG, the lepromin test converted to positive among the clinically subsided, skin smear-negative lepromatous patients, but this vaccination did not effect the protective immunity.

In 1957, Indian scholars separated a culturable AFB (ICRC bacteria) from LL patients which could induce the cell-mediated immune response to the leprosy bacilli among laboratory animals and humans. After separation from LL patients in 1969, multifamilial culture *in vitro*, γ-ray inactivation and finally intracutaneous injection at the dosage of 0·1 ml (50–90 μg bacilli), 55·7% LL and 91% BB–BL converted to lepromin test positive, and 5 out of 46 cases showed reversal reaction.

In addition to ICRC bacteria, Indian scholars used a heat-killed vaccine named W bacillus, an atypical, quick growing bacillus that had been separated from the sputum of tuberculotic patients. They selected 32 BL–LL leprosy patients, who had negative skin-smears after chemotherapy, and intracutaneously injected normal saline containing 5×10^7 bacilli and 20 cases converted to lepromin test positive after 4–6 weeks, and the positivity lasted beyond 6–11 months.

In the 1970s, Convit *et al.* claimed that the combined vaccine (consisting of HKML plus BCG) was both acceptable and effective as a treatment for leprosy patients, but it is unclear how the combined vaccine activates the protective immunity of the lepromatous leprosy. Recently immunological study has confirmed that the mechanism was complicated. *In vitro* T-lymphocytes of the lepromatous patients lack a normal response to leprosy bacilli, and the deficiency of interleukin-II may be a factor, related to the activation of the suppressor cells. Lepromatous patients have a normal response to BCG, so the immunotherapy acts like a source supplying interleukin-II, a pathway making good the deficiency of the patients. Also, the macrophages activated by BCG might be changed noticeably in managing and passing the antigen, which produce effective protective cell-mediated immune reaction.

Since 1990 we have selected 30 patients for the trial who had a combined vaccine of HKML plus BCG, and all skin-smear negative after the treatment of MDT. There were 8 injections in the trial. The main local skin reaction was a tolerable ulceration, but systemic reaction, including iridocyclitis, and a numbness of fingers and toes, gradually increased after the 5th injection. The iridocyclitis had obvious opthalmological manifestation, but the latter had no objective positive signs, although the patients complained of numbness. All the complaints subsided after antisymptomatic treatment. During the trial, neither ENL nor reversal reaction was found.

After the 8th injection, 66·7% cases converted to Mitsuda reaction positive. Histopathological examination showed tuberculoid infiltration surrounding the vessels in deep reticular stratum, which demonstrated that specific cell-mediated immune response to leprosy bacilli was repaired and reinforced among two-thirds of patients in the trial. Combined chemotherapy plus vaccine injection might facilitate the clearance of the leprosy bacilli in the host, reduce relapse and shorten the duration of skin-smear negativity.

Acknowledgment

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express their gratitude to Dr K. V. Desikan for his assistance in histopathologic confirmations of the Mitsuda reactions.

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Une étude pilote pour déterminer l'acceptabilité du vaccin tué par la chaleur de *Mycobacterium leprae* plus BCG (HKML + BCG) et son aptitude a faire virer la cuti-réaction

CHEN ZAI-LING, TANG QUAN-GUI, WANG ZAI-MING ET CHEN JIAKUN

Résumé Bien que des réactions locales, comprenant érythème; induration et ulcères, soient apparues chez tous les patients après l'injection du vaccin combiné HKML + BCG, cette injection a été bien acceptée par les patients. Il n'y a pas eu tendance à l'aggravation des réactions locales après des vaccinations répétées. Pourtant, la fréquence des réactions systémiques, en particulier l'irido-cyclite et celle des patients se plaignant d'engourdissement des doigts et des orteils ont augmenté après la 5ème vaccination et ont réduit l'acceptabilité de la 6ème injection. Il semble que la vaccination répétée puisse activer l'irido-cyclite, mais la correlation entre la plainte d'engourdissement et la vaccination n'a pas été prouvée. Ni ENL typique ni réaction de réversion n'ont eté observés au cours de cet essai.

Une proportion significative des patients sont devenus SMLA-positifs après la vaccination répétée. Pourtant, il semble que cette positivité ne soit pas stable car beaucoup d'entre eux sont redevenus négatifs après la vaccination suivante. Après la 7ème vaccination, le taux de positivation à SMLA-I a été de 45% et à SMLA-II de 35%. Après la 8ème vaccination, 66,7 des patients sont devenus positifs à la réaction de Mitsuda, ce qui a été confirmé par examen histopathologique. Mais il faudra continuer à suivre ces patients pour déterminer si cette conversion sera de longue durée ou passagère.

Les réactions à SMLA-I et SMLA-II ont été associées mais la corrélation était d'un niveau moyen. Au total, la positivation à SMLA-I a été sensiblement plus élevée que celle à SMLA-II après la vaccination répétée. Ni la réaction précoce ni la réaction tardive au test de la lépromine (Mitsuda) n'a présenté de corrélation avec l'une ou l'autre des réactions à SMLA.

La vaccination répétée au vaccin HKML + BCG n'a pas modifié le taux d'anticorps anti-PGL-I *Mycobacterium leprae* faiblement positif observé chez les patients lépromateux à frottis de peau négatif participant à cette étude.

Un estudio piloto para establecer la aceptabilidad y habilidad de *Mycobacterium leprae* matados por calor más vacuna BCG (HKML + BCG) para inducir conversión de la prueba dérmica

CHEN ZAI-LING, TANG QUAN-GUI, WANG ZAI-MING Y CHEN JIAKUN

Resumen Aunque reacciones locales, incluyendo eritema, induración y úlceras, aparecieron en todos los pacientes después de la inyección de vacuna (HKML + BCG), aquellas fueron aceptados por los pacientes. No hubo tendencia para que se agrave la reacción local después de repetir la vacunación. Sin embargo, las reacciones sistémicas, principalmente iridociclitis y quejas de adormecimiento de los dedos de las manos y pies, eran bastante comúnes despues de la 5a. vacunación y, por lo tanto, reducen la aceptabilidad de vacunación por inyección significativamente. Parece que la vacunación repetida puede activar la iridociclitis, pero no se ha establecido bien la relación entre el adormecimiento y la vacunación. Durante el estudio no se observó una ENL típica ni una reacción inversa.

Una proporción significativa de pacientes cambiaron a positividad SMLA después de vacunación repetida. Sin embargo, parece que el estado positivo no era estable ya que muchos de ellos revirtieron a negativo despues de la vacunación siguiente. Después de la 7a. vacunación, el nivel de conversión positiva a SMLA-I fue 45%, y a SMLA-II 35%. Después de la 8a. vacunación, 66,7% de los pacientes convierteron a una reacción Mitsuda positiva, confirmada por un examen histopatológico. No obstante, será necesario un estudio posterior para establecer si la conversión será de largo plazo.

Las reacciones a SMLA-I y SMLA-II estaban asociadas, pero solamente correlacionaban en un nivel moderado. En total, el nivel de conversión positiva a SMLA-I era significativamente más alta que la conversión a SMLA-II después de vacunación repetida. Ni la reacción anterior ni la posterior (Mitsuda) de la prueba de lepromina correlacionaban con las reacciones SMLA.

La vacunación repetida con vacuna (HKML + BCG) no afectó el nivel de anticuerpos anti-PGL-1 de *Mycobacterium lepræ* observado en los pacientes lepromatosos con smear de la piel negativo.