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Long-Term Follow up of Lepromatous Leprosy Patients Receiving Intralesional Recombinant Gamma-Interferon

TO THE EDITOR:

The primary defect in lepromatous leprosy is probably the lack of generation of sensitized T cells ([1]) which results in deficiency of gamma-interferon (IFN-γ) in the lesion ([5]). Macrophages in the tissue as well as in the circulation of lepromatous patients remain functionally normal because they release oxygen intermediates when activated by IFN-γ and other antigens ([3]). Kaplan, *et al.* in their study on the effect of intralesional recombinant IFN-γ (rIFN-γ) have demonstrated the accumulation of lymphocytes and monocytes, marked thickening of the epidermis, and increased expression of Ia and γ-IP-10 at the site of injection. With repeated injections of rIFN-γ there was a reduction in OKT-6 cells in the dermis and a distinct fall in the tissue bacterial index (BI) (5,000–10,000-fold) at the site of injection. This was often associated with the formation of an epithelioid granuloma with multinucleated giant cells ([2, 4]). The local changes prompted us to follow these cases to see whether intralesional rIFN-γ also influences tissue response at distant sites.

Twenty-two lepromatous leprosy patients (15 LLp, 7 LLs) were included in this study. There were 18 males and four females whose ages ranged from 23–58 years. Out of these 22 patients, six cases were untreated and 15 cases were on treatment for less than 1 year. Only one patient was on antileprosy drugs for more than 5 years. Lyophilized rIFN-γ (Boehringer, Ingelheim am Rhein, Germany) specific activity 2×10^7 U/mg protein was diluted and 10 μg IFN-γ in 100 μl of excipient was injected at the lesional site. The number of such injections in an individual patient varied from 1 to 3 or more. If a patient received more than one injection, it was on consecutive days and into the same lesion.

Patients were subjected to clinical charting, slit-skin smear, skin biopsy, and lepromin testing initially and then at an interval of 3–6 months for 18 months. All patients were on conventional multidrug therapy (MDT) throughout the study.

The clinical response in all 22 patients was similar to what we observe with conventional MDT in our clinic. None showed evidence of clinical or histological upgrading or lepromin conversion. Severe erythema nodosum leprosum (ENL) was observed in four patients and mild-to-moderate ENL was seen in seven patients. In two patients neural pain was aggravated.

The average fall in the BI was of 1.0 (Ridley's scale) after 18 months of follow up. Histological examination revealed that the reduction in the size of the granuloma was 1.16 and the fall in the granuloma BI was 1.01 after 18 months of follow up (The Table).

The nature of the infiltrate was predominantly of the macrophage type, and the influx of lymphocytes was insignificant up to

THE TABLE. *Clinical and laboratory follow up on patients receiving IFN-γ.*

Age	sex	Duration of MDT (mo.)	No. and dosage of IFN-γ (x μg)	Slit-skin smear BI		Tissue BI		Granuloma size	
				Initial	18 mo.	Initial	18 mo.	Initial	18 mo.
			2 × 10						
35	M	12	2 × 10	6+	5+	5+	4+	4+	2+
23	M	NT[a]	2 × 10	6+	5+	6+	4+	5+	4+
32	M	10	2 × 10	5+	4+	5+	4+	4+	3+
45	M	NT	2 × 10	5+	4+	4+	NA[b]	5+	2+
44	F	01	2 × 10	5+	5+	6+	5+	5+	5+
38	M	05	2 × 20	5+	4+	5+	4+	4+	3+
55	M	60	2 × 20	3.5+	1+	2+	Neg.	3+	NA
55	M	02	2 × 20	3.5+	2.75+	4+	1+	2+	3+
30	F	05	2 × 20	3+	1+	4+	2+	3+	2+
40	F	07	2 × 20	4+	2+	3+	2+	3+	2+
30	M	10	3 × 10	5.5+	5+	5+	3.50+	5+	3+
23	M	NT	3 × 10	5+	5+	5+	5+	5+	1+
40	M	12	3 × 10	4.75+	4+	5+	5+	3+	4+
35	M	09	3 × 10	5+	4+	5+	4+	3+	1+
50	M	07	3 × 10	5+	3+	5+	4.25+	5+	NA
58	M	18	5 × 10	5.5+	4+	5+	4+	3+	2+
40	M	12	3 × 10	5.5+	5+	NA	4+	5+	4+
28	M	09	3 × 10	5+	5+	5+	4.0+	2+	1+
45	M	NT	3 × 10	4.75+	NA	5+	4.5+	5+	3+
37	M	NT	3 × 10	4+	3+	5+	3.75+	NA	2+
55	M	NT	3 × 10	5+	4.5+	5+	5+	NA	3+
30	M	05	3 × 10	4+	NA	4+	NA	5+	2+

[a] NT = Not treated.
[b] NA = Not available.

1 year. A noticeable increase in lymphocytes was observed in the biopsies of 18 months' follow up. It was conspicuous that lymphocytic influx was seen more in LLs than in LLp patients. The number of injections of IFN-γ also had no influence on the above parameters.

From this study it can be inferred that in spite of bacterial killing at the site of the rIFN-γ injection by the host macrophages (release of antigenic components) in the presence of large quantities of Ia molecules and T4 cells, the process of primary sensitization could not be initiated. This suggests that in the LL form of the disease there must be some very effective, specific suppressive mechanism or clone deletion which prevents primary sensitization. We are tempted to compare this situation with the studies carried out in the field of contact sensitization, where when an animal was made unresponsive to trinitrophenyl (TNP) by challenging through the intravenous route, the animal remained unresponsive in spite of repeated intradermal injection of TNP ([6]). We feel that more research is needed for the understanding of the development of specific unresponsiveness and responsiveness in leprosy.

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Subgroups Among Lepromatous Leprosy—A Viewpoint

TO THE EDITOR:

In the recent past it has been observed that all lepromatous leprosy cases do not show uniformity in the generation of gamma-interferon in response to concanavalin A (conA), *Mycobacterium leprae,* and BCG ([2]). Similarly, in various vaccine trails nearly 30%–40% of the patients failed to show lepromin conversion ([1]). These parameters suggest that the lepromatous leprosy (LL) cases are immunologically heterogenous, and there is a possibility that there might be subgroups among lepromatous leprosy cases ([4]). In our leprosy clinic we have observed that some of the LL patients develop the LL form *de novo*; whereas some acquire the LL form by gradual downgrading from a higher position in the spectrum of the disease. In the present study an attempt has been made to characterize these two subgroups on the basis of the a) history of evolution of the disease, b) clinical presentation, c) bacteriological status, d) histology, and e) lepromin test.

Fifty-three patients were included in this study, 46 (86.8%) were males and seven (13.2%) females. Their ages ranged from 18 to 75 years. The lepromin test was negative in all. From the analysis of our data, two distinct patterns have emerged. In 29 patients (Group I) none had discrete lesions suggestive of a higher position in the leprosy spectrum in the past or at the time of examination. All patients showed generalized diffuse infiltration; 12 (41.4%) also had nodulation, 20 (69%) had symmetrical peripheral neuropathy, 19 (65.5%) had edema of the hands and feet, eyebrows were intact in 13 (44.8%), ichthyotic changes in skin of the lower extremities were seen in 14 (48.3%), evidence of erythema nodosum leprosum (ENL) was seen in 3 (10%), and only 3 (10%) patients had trophic ulcers. In the remaining 24 patients (Group II) history of onset of disease suggested that the initial lesion in 12 patients was an erythematous plaque, 6 had maculoanesthetic patch(es), 3 noticed symptoms of neuropathy, 2 had pain in nerve, and 1 observed nodules. On examination, in addition to lesions suggestive of lepromatous leprosy, 17 (70.8%) had a few skin lesions suggestive of a higher portion of the leprosy spectrum (BT, BB and BL), 14 (58.3%) had peripheral neuropathy, 6 (25%) had evidence of neuritis, deformities were seen in 7 (29.2%), generalized infiltration in 2 (8.3%), nodular lesions were seen in 6 (25%), eyebrows were intact in 10 (41.7%), and 6 (25%) had ENL.

The bacterial index (BI) in the slit-skin smears from four sites was uniformly high (5–6+) in Group I, and there was a good correlation with tissue BI. In Group II, the smear as well as the tissue BI showed significant variations from site to site.

To study the nature of the cellular infiltrate, biopsies were taken from three sites. In Group I, since they had generalized diffuse infiltration, biopsies were taken from a) one of the extremities, b) the trunk, and