Comparison of Pentoxifylline, Thalidomide and Prednisone in the Treatment of ENL

TO THE EDITOR:

Erythema nodosum leprosum (ENL) is an inflammatory reaction that occurs in approximately 40%–50% of lepromatous leprosy patients, most commonly during treatment with antileprosy drugs. ENL is characterized by the appearance of painful, erythematous, subcutaneous nodules which are tender to the touch. These lesions are not necessarily associated with pre-existing leprosy lesions. Systemic manifestations including fever, malaise, lymphadenopathy, neuritis, and arthralgia are often observed. It appears that the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α) may play an important role in the development of this syndrome since high plasma levels of TNF-α are found in patients during episodes of active ENL ([10]). Moreover, treatment of ENL patients with thalidomide alleviates the clinical symptoms concomitant with a reduction in plasma TNF-α levels ([8]). *In vitro,* thalidomide selectively inhibits the production of TNF-α by lipopolysaccharide-stimulated monocytes ([6, 9]).

Although thalidomide is the drug of choice for the treatment of ENL ([3, 7, 12, 13]) it is a potent teratogenic drug ([4, 5]) and is not safe in women of child-bearing potential. Glucocorticoids, a family of drugs known to inhibit cytokine production by leukocytes, are also used for the treatment of ENL. Unfortunately, the prolonged use of these drugs is associated with toxicities, including immunosuppression. In an attempt to identify other treatments for ENL, alternative TNF-α inhibitors are under consideration. One such drug is pentoxifylline, a methylxanthine derivative which has been used clinically for intermittent claudication. The drug has been shown to inhibit TNF-α production *in vitro* ([2, 14]) and *in vivo* ([1, 8]).

We have now tested whether pentoxifylline if effective in alleviating the signs and symptoms of ENL and have compared the efficacy of the drug in controlling the symptoms and dermatologic manifestations of ENL to the efficacy of thalidomide and of steroids. Sixteen multibacillary leprosy patients with ENL were graded for severity of disease symptoms at the start of the study and weekly thereafter (The Table). Plasma was collected at baseline and weekly for cytokine evaluation, and biopsies of ENL lesions were taken at baseline and day 2 for histologic evaluation of the response in the skin.

RESULTS AND DISCUSSION

Clinical response. The manifestations of ENL were graded for severity of disease

THE TABLE. *Characteristics and treatment regimens for multibacillary leprosy patients with ENL.*[a]

Patient no.	Age	Sex	Severity of ENL		Treatment
			Day 0	Day 21	
1 (JG)	21	M	1	0	Pent 1200
2 (GO)	26	M	2	0	Pent 1200
3 (JT)	23	F	2	0	Pent 1200
			2[b]	1	Prednisone
4 (DP)	26	M	2	0	Pent 1200
5 (SC)	28	M	2	0	Pent 1200
			1[b]	0	Prednisone
6 (BL)	32	M	1[c]	Interrupted	Pent 1200
			3	0	Thalidomide
7 (RM)	25	M	2[c]	Interrupted	Pent 1200
			2	0	Thalidomide
8 (ES)	26	M	2[c]	Interrupted	Pent 1200
			2	0	Prednisone
9 (RA)	23	M	1[c]	Interrupted	Pent 1200
			1	0	Prednisone
10 (RS)	16	F	2	1	Pent 2400
11 (RV)	36	M	3	0	Pent 2400
12 (MR)	23	M	2	1	Pent 2400
			2[b]	1	Prednisone
			2[b]	0	Thalidomide
13 (RM)	23	M	2	0	Pent 2400
			2[b]	0	Prednisone
14 (JP)	22	M	3	0	Thalidomide
15 (JL)	22	M	3	0	Thalidomide
16 (HT)	18	M	3	0	Thalidomide

[a] All patients were outpatients at the Leonard Wood Memorial Leprosy Clinic, Cebu, The Philippines, and were treated with standard WHO multidrug therapy supplemented with: Pent 1200-pentoxifylline 1200 mg/day; Pent 2400-pentoxifylline 2400 mg/day.

[b] Patients who developed a new ENL episode 3–4 months after completion of therapy and re-entered the study on a different treatment regimen.

[c] Patients who failed to respond within 7–10 days after initiation of treatment and were then switched to another drug.

symptoms and to enable us to evaluate the therapeutic responses, according to the outline in the legend of The Figure. Of the 16 ENL patients included in the study, nine patients received 1200 mg/day of pentoxifylline (The Table). The mean grade of ENL for these patients was 1.7 ± 0.5 (mean ± S.D.).

Five out of the nine patients treated with 1200 mg/day of pentoxifylline responded to the treatment with clinical improvement and relief of symptoms such as fever, headaches and joint pain by 2 weeks (The Figure). However, flattening or clinical clearance of the ENL skin lesions was observed only during the third week of therapy. Despite clinical improvement in response to treatment with 1200 mg/day of pentoxifylline, the skin lesions of some patients did not disappear or appeared even worse histologically with increased inflammatory infiltrate and a thicker epidermis. In the four patients who did not respond to the regimen of 1200 mg/day pentoxifylline, treatment was interrupted because the patients developed new ENL lesions with worsening of symptoms (The Table).

To evaluate whether the lack of response to 1200 mg/day of pentoxifylline therapy could be overcome by a higher dose of the drug, four new patients (patients 10 to 13) with a mean ENL severity of 2.3 ± 0.5 were treated with 2400 mg/day of pentoxifylline. By 4 to 5 days of therapy these patients reported subjective improvement of clinical symptoms, and by day 14 there was improvement of the ENL lesions. However, at day 21, two of these patients still had grade 1 ENL lesions, although they manifested no systemic clinical symptoms (The Figure).

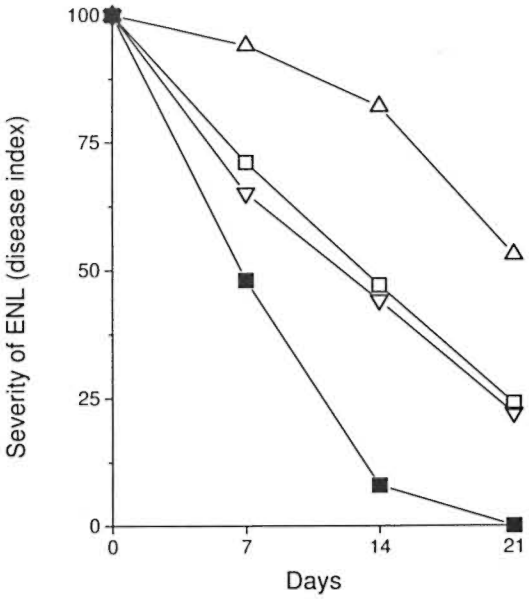
To compare the patient response to pentoxifylline with the patient response to tha-

lidomide, six patients were treated with thalidomide. Patients received 300 mg/day of thalidomide for the first 7 days followed by 200 mg/day of thalidomide for 7 days followed by 100 mg/day of thalidomide for the last 7 days, a total of 21 days of treatment. Three patients (patients 14–16) were entered directly into the thalidomide treatment group, two patients (patients 6 and 7) were shifted to this drug because they failed to respond to treatment with 1200 mg/day of pentoxifylline, and one patient (patient 12) suffered a relapse of ENL after successful completion of therapy with 2400 mg/day pentoxifylline (The Table; The Figure). The mean grade of ENL for these patients was 2.5 ± 0.5. Clinical improvement was observed as early as 2–4 days after initiation of thalidomide therapy and by day 14, 5/6 patients showed clinical remission. No ENL lesions were observed in the thalidomide treated patients at day 21. As seen in The Figure, the clinical response to therapy with thalidomide occurred earlier than the response observed with the other treatment regimens.

Prednisone (30 mg/day) was used to treat six ENL patients. Two patients (patients 8 and 9) first treated with 1200 mg/day of pentoxifylline were switched to prednisone (The Table) and four patients with relapsing ENL (patients 3, 5, 12, and 13) subsequently received prednisone. Following 21 days of therapy with prednisone, 4/6 patients showed remission of ENL symptoms and lesions (The Figure).

No adverse effects were observed with the use of any of the drugs.

Plasma cytokine and cytokine receptor levels. At the time of initiation of treatment for ENL, the mean TNF-α plasma level for all patients tested was 43 ± 10 pg/ml (ranging from 6 to 159 pg/ml), the mean soluble TNF-αR level was 8.6 ± 0.8 ng/ml (ranging from 3 to 16.3 ng/ml), and the mean soluble IL-2R level was 2125 ± 273 pg/ml (ranging from 662 to 4194 pg/ml). In patients treated with either dose of pentoxifylline, there was no reduction in the plasma levels of TNF-α, soluble TNF-αR, or IL-2R. In fact, a twofold increase in TNF-α levels and a slight increase in the levels of TNF-αR and IL-2R was observed in response to pentoxifylline. This cytokine response occurred regardless of whether or not the patients showed a clinical response to pentoxifylline treatment. In contrast to the pentoxifylline-associated increase in cytokines, the thalidomide treatment of ENL patients was associated with a 53% reduction in plasma TNF-α levels by 21 days postinitiation of therapy, as has been described previously ([8, 10]). Soluble TNF-αR was reduced by 50% and IL-2R was reduced by 43%. When ENL patients were treated with prednisone, there was an 84% decrease in the levels of TNF-α. Soluble TNF-αR was reduced by 44% and IL-2R was reduced by 37% at 21 days postinitiation of prednisone therapy.



THE FIGURE. Clinical response of ENL patients to the different therapeutic regimens. Manifestations of ENL were graded for severity of disease symptoms and to evaluate the therapeutic responses, according to the following criteria: Grade 0 = no ENL lesions; grade 1 = patients with <10 ENL lesions, usually without fever or other symptoms (these lesions were usually discovered during routine physical examination); grade 2 = patients with 10 to 20 ENL lesions who presented with mild fever, recurrent ENL, and often mild neuritic pain; grade 3 = patients with >20 ENL nodules, lesions with blebs or pustules or ulcers, daily fevers and other symptoms such as headaches, myalgia and anorexia. Results are mean grade of ENL observed in the patients evaluated during therapy expressed as percentage (day 0 or time of diagnosis = 100%). △ = response to 1200 mg/day of pentoxifylline; ▽ = response to 2400 mg/day of pentoxifylline; □ = response of patients treated with prednisone; ■ = response of patients treated with thalidomide.

There was no correlation between severity of ENL symptoms and the starting plasma levels of cytokine or cytokine receptors.

Since relatively low levels of TNF-α were detected in the plasma of the patients with active ENL in this study, the results suggest that TNF-α may not be the only factor in the pathogenesis of ENL. In fact, prednisone reduces TNF-α levels more efficiently than thalidomide, but the clinical response to the prednisone is somewhat slower than that observed with thalidomide treatment. Recent studies have suggested that thalidomide may also act as an immunostimulator, inducing the secretion of IL-2 by T cells ([11]). Whether thalidomide acts to stimulate T-cell activity in ENL patients, and the possible implications of such a stimulus on the course of ENL, remains to be determined.

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