TABLE 2. *Relapses in PB leprosy.*

Study	No. of patients	Follow-up (years)	No. of relapses	%	Annual rate %	Person years (PY)	Relapse/ 1000 PY
			ROM-1 for PB (2–5) leprosy				
Revankar, *et al.* (current study)	335	2.8	5	1.4	0.5	940	5.3
			WHO-PB MDT for PB leprosy[a]				
Li, *et al.* (1997) [1]	2,326	5	5	0.2	0.04	9,111	0.55
Indonesia WHO (1995) [4]	471	5	3	0.6	0.12	2,500	1.2
Malawi WHO (1995) [4]	484	4	12	2.5	0.63	2,000	6.0
Multicenter study WHO (1995) [4]	51,553	9	306	0.6	0.07	319,381	0.96

[a] Also includes single skin lesion-paucibacillary SSL-PB Leprosy.

The annual relapse rate (0.5%) in the ROM-1 treated PB (2–5) leprosy group is more or less comparable to the already reported annual relapse rate in the PB-MDT treated group (Table 2). This follow-up study indicated that ROM-1 dose in PB (2–5 lesion group) appears to be adequate because the relapse rate is well within acceptable limits and comparable to the PB-MDT treated group.

—C. R. Revankar
H. O. Bulchand
V. V. Pai
R. Ganapati

Bombay Leprosy Project
11, VN Purav Marg, Chunabhatti
Bombay-400022, India

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A Phase 2 Open Trial of Pentoxifylline for the Treatment of Leprosy Reactions

TO THE EDITOR:

Pentoxifylline (PTX) is an immunomodulatory agent with rheologic properties.([11]) It diminishes the effect of TNF-α and IL-1 on polymorphonuclear cell (PMN) chemotaxis, adhesion and toxic radical formation. ([23, 24, 3]) PTX may modulate endothelial adhesion receptors leading to reduced PMN adhesion. ([8]) PTX has been shown to inhibit TNF-α production at both mRNA and protein levels in murine macrophages. ([22, 4]) On the other hand, PTX has little effect on IL-1 and IL-6 production but decreases induced leukocyte responsiveness. ([5, 27]) PTX inhibits human dermal fibroblasts *in vitro* and the production of collagen, glycosaminoglycan and fibronectin. ([2]) PTX also has a suppressive effect on natural killer cells. ([13]) PTX is thought to operate in part by increasing intracellular cyclic AMP. ([18, 16]) Thalidomide is another agent that inhibits TNF-α production which it does by enhancing the degradation of TNF-α mRNA. ([10]) Thalidomide has been used extensively along with corticosteroids in the treatment of erythema nodosum leprosum (ENL) in Hansen's disease. ([17]) Thalidomide is well-known for its teratogenic effects.

Hansen's disease is a chronic mycobacterial disease marked by multifaceted immunologic involvement in its pathogenesis. The spectrum of Hansen's disease is classified according to Ridley and Jopling into five categories. ([15]) The disease status is further complicated by different reactional states mainly erythema nodosum leprosum (ENL) and reversal reaction (RR). Clinically ENL is characterized by development of crops of new, small, tender subcutaneous nodules, which usually subside after a few days along with systemic features like

pyrexia, arthralgia, neuritis, and adenopathy. RR, on the other hand, presents as brawny, indurated, erythematous skin plaques with neuritis. TNF-α is thought to be a key mediator in Hansen's disease and reactional states. ([2, 13, 18]) It has been suggested that PTX may be beneficial in Hansen's disease reactions. ([16]) Because PTX inhibits TNF-α, transcription and production and because TNF-α has been implicated as a major mediator of leprosy reactions, we evaluated the effect of PTX in the treatment of leprosy reactions.

Patients were selected from the New York Regional Hansen's Disease Clinic, after obtaining Institutional Review Board-approved informed consent. Patients were classified according to Ridley and Jopling. ([15]) All leprosy patients with reactions were evaluated and eligible for entry into the study. Reactional states were identified and classified according to patients' symptoms and signs and in some patients according to their skin biopsy. Patients were randomly assigned to different treatment regimens of PTX ranging between 1200 mg to 2400 mg in divided doses. If patients were already on therapy for reactional states with corticosteroids, they were recruited if reactional states worsened with that dose and, rather than increasing the steroid, PTX was added. Patients were followed by one observer (Dr. William Levis) for evaluation of responses, which were determined at each clinic visit (average 4 assessments per patient). The range of time on PTX was from 0.8 months to 16.3 months with a median of 8.3 months.

Responses were defined into five categories with a descriptive and numerical value. Definition of responses: excellent (5)–complete resolution of all symptoms and signs; good (4)–resolution of most symptoms and signs but persistence of some minimal features; fair (3)–resolution of some symptoms and signs but persistence of most features; no response (2)–no effect of therapy on symptoms and signs; and worse (1)–worsening of symptoms and signs after initiation of therapy. Statistical analysis of the scaled response was done using the nonparametric test of differences, the Mann Whitney and the Fisher's Exact Probability Test.

A total of 21 patients completed the study. The age range of the patients varied between 22 years to 79 years. All the patients in the study were born outside the United States. Table 1 gives the classification and demography of patients. Of the 21 patients, 16 were lepromatous or borderline lepromatous and 5 patients were tuberculoid or borderline tuberculoid. Thirteen among the 21 patients had reversal reaction (RR) and 8 patients had erythema nodosum leprosum (ENL). Patients were treated with PTX in a dose range of 1.2 gm to 2.4 gm in three or four divided doses. Table 2 gives the response of leprosy reactions to PTX therapy. Of the 8 patients with ENL, 5 patients (62.5%) had fair responses, 2 patients (25%) had good responses, and 1 patient's (12.5%) reaction worsened. Among 13 patients with RR, 5 patients (38%) had fair responses and 1 patient (8%) had a good response, 4 patients (30%) had non-response and in 3 patients (24%) their reaction worsened. None of the patients had excellent responses. Response to PTX was considered from the scaled score with a range of 4 to 1. Four was considered a good response, 3 was a fair response, 2 was a non-response, and 1 was a worsening response. The scaled responses were analyzed by the Mann Whitney test of differences for non-parametric testing. No significant differences were noted between the ENL and RR on response ($p < 0.15$) with a Z value –1.41. This result was also noted when the ENL and RR groups were divided into responders (good or fair) and non-responders (non- or worse). The ENL group had 7 responders and 1 non-responder. The RR group had 7 responders and 6 non-responders. The Fisher's exact probability test was used to examine the differences between groups and the result was non-significant at $p \leq 0.17$. Spearman's rho was used to test the correlation between response and dose, as response rates were ordinal data (ranked scoring) and more appropriate for non-parametric testing. The higher the dose, the lower the scaled response. Therefore, higher doses were moderately, negatively correlated with lower responses. Spearman's rho –0.48.

Table 3 shows the side effects associated with PTX therapy. Seven patients receiving PTX had side effects ranging from nausea, abdominal discomfort, headache and dizzi-

TABLE 1. *Demography and clinical classification of leprosy patients with ENL & reversal reactions (RR).*

Patient	Country of origin	Age	Sex	Classification	Reactional states	Other therapy
1	India	22	M	LL	ENL	Prednisone 10 mg QOD,[a] Dapsone, Clofazimine 50 mg BIW[b]
2	India	34	M	LL	ENL	Prednisone 30 mg QOD, Dapsone
3	Ecuador	65	F	BL	ENL	Prednisone 30 mg QD,[c] Dapsone
4	Brazil	28	F	LL	ENL	Clofazimine 50 mg CWK[d]
5	Dominican Republic	36	M	LL	ENL	Dapsone, Clofazimine 100 mg QD
6	Philippines	28	M	BL	ENL	Dapsone, Rifampin
7	India	39	F	BL	ENL	Dapsone
8	Philippines	79	F	LL	ENL	Rifampin, Clofazimine 100 mg QD
9	Brazil	32	F	BL	RR	Dapsone, Clofazimine 50 mg BIW
10	Thailand	43	M	LL	RR	Dapsone
11	Panama	23	F	LL	RR	Dapsone, Clofazimine 50 mg QD
12	Haiti	25	F	LL	RR	Clofazimine 50 mg QD
13	Guyana	49	M	LL	RR	Dapsone
14	Surinam	34	M	LL	RR	Dapsone
15	Philippines	24	F	BT	RR	Dapsone
16	Cuba	50	M	BT	RR	Dapsone, Prednisone 30 mg
17	Philippines	27	M	BT	RR	Dapsone
18	Dominican Republic	40	F	TT	RR	Dapsone, Prednisone 40 mg
19	Dominican Republic	39	F	BT	RR	Dapsone
20	Philippines	67	M	BL	RR	Dapsone, Clofazimine 50 mg QD
21	Guyana	31	M	LL	RR	Dapsone

[a] QOD = every other day.
[b] BIW = twice weekly.
[c] QD = every day or daily.
[d] QWK = once weekly.

TABLE 2. *Clinical response of leprosy reactions to Pentoxifylline.*

Reactions	Excellent	Good	Fair	None	Worse
LL					
ENL(5)	—	1	3	—	1
RR(6)	—	—	2	2	2
BL					
ENL(3)	—	1	2	—	—
RR(2)	—	—	1	1	—
BT					
ENL(0)	—	—	—	—	—
RR(4)	—	1	2	1	—
TT					
ENL(0)	—	—	—	—	—
RR(1)	—	—	—	—	1

TABLE 3. *Side effects of Pentoxifylline in patients with ENL or reversal reactions.*

Patient no.	Side effects[a]
2	Nausea, vomiting
10	Right upper quadrant abdominal pain
13	Nausea, abdominal discomfort
17	Headache
18	Headache, dizziness, palpitation
19	Nausea, abdominal discomfort
20	Mild dizziness

[a] Dose of 400 mg 3 times per day was better tolerated than higher doses, but some nausea and vomiting occurred at lower doses.

ness. PTX had to be discontinued in three patients (patients 2, 10 and 13). One patient (19) tolerated PTX after lowering the dose. The other three patients had minimal symptoms and did not require alteration of therapy. Spearman's rho = 0.31 for the correlation between dose and side effect. The result is a weak positive correlation. The higher doses appear to be positively correlated with the increased incidence of side effects.

Our results suggest that PTX may have some minimal efficacy in the treatment of reactional states in Hansen's disease possibly due to inhibition of TNF-α production. Mycobacterial lipoarabinomannan (LAM) has been shown to stimulate TNF-α and nitric oxide (NO) synthesis in mouse macrophages. ([20]) LAM also has immunosuppressive effects like inhibition of T-cell proliferation. ([9]) There is a wide spectrum of immunological manifestations seen in Hansen's disease. LL type is characterized by low cellular immunity and high TNF-α level and they frequently have ENL type of reaction, ([21]) partly due to the increased release of LAM and subsequent induction of TNF-α and inhibition of cellular immunity. TT-BT types on the other hand have increased cellular response, lower TNF-α level and they frequently have RR type of reaction. ([13, 18, 16]) In our study we did not see a statistically significant better result in ENL, but there was a hint of greater response in ENL.

Eight (38%) of our patients were on clofazimine and all the patients were on dapsone. The precise role played by dapsone and clofazimine is not clear yet. They may have variable effects on eicosanoids, ([1]) but since patients developed reactional states even with clofazimine and dapsone it indicates they probably do not play an important role. All the patients in our study were followed by one observer, thereby, eliminating inter-observer variability in this complex disease. Overall patients in our study did not respond to PTX as well as we had hoped. Six out of 21 patients (29%) subsequently required prednisone or an increased dose of prednisone.

PTX has been noted to be an incomplete inhibitor of TNF-α. ([19]) Unlike corticosteroids, PTX has not been shown to affect the eicosanoid pathway of inflammation. ([26]) Eicosanoids are thought to be terminal mediators of cell injury. TNF-α induces the synthesis of eicosanoids ([7]). In experimental models inhibition of eicosanoids has attenuated TNF-α mediated sepsis. ([6]) In this regard we have found zafirlukast, a leukotriene 4 receptor antagonist, to be more promising as a nonsteroidal treatment for leprosy reactions than PTX. ([26]) We have also found PTX to be a poor inhibitor of nitric oxide (NO) production. ([14]) The poor inhibition of NO, coupled with incomplete inhibition of TNF-α and failure to affect the eicosanoids could account for the breakthrough and worsening of reactions found in up to 20% of the subjects with ENL. ([12]) At this time, considering the large number of nonsteroidal anti-inflammatory agents currently in development we would recommend pursuing agents other than PTX as alternatives for the treatment of leprosy reactions.

—Zubaer M. Dawlah, M.D.[1]
Aloys Cabrera, R.N. P.H.N.[1,2]
Kathleen Ahern, Ph.D., R.N.[1]
William R. Levis, M.D., Director[1,2]

[1] *Staten Island University Hospital*
New York City—Regional Hansen's Disease Program
475 Seaview Avenue
Staten Island, New York 10305

[2] *Bellevue Hospital-NYU Medical Center*
New York City—Regional Hansen's Disease Program
462 First Avenue & 27th Street
New York City, NY 10016

Address for reprint request: William R. Levis, M.D., Director Bellevue Hospital—Hansen's Disease Program

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Successful Treatment of the Paralyzed Lower Eyelid Due to Hansen's Disease by Implanting Auricular Cartilage

TO THE EDITOR:

We performed auto-auricular cartilage implants into the paralyzed lower eyelids of some former Hansen's disease patients, who live in our National Sanatorium, in order to improve upon the conditions of lagophthalmos and/or ectropion, due to facial nerve paresis. Sixty-nine eyelids of 50 patients: 34 men and 16 women, from 48 to 88 years of age (74-year-old average) were operated on during a 4½ year period from November 1996 to April 2001. They had complained of eye pain and dryness, spilling out of tears (epiphorea), complications in the treatment of corneal wounds, and ill-fitting artificial eyeballs caused by their lagophthalmos and/or ectropion.

Their facial paresis had persisted over a long period of up to 40 years or more. Some patients had already received another operative procedure, such as partial eyelid suturing or fascial implantation into the eyelids. They may have had some temporary improvement, but the effect could not be maintained.

Some of the skin conditions to be considered were that ex-lepromatous or borderline lepromatous patients' facial skin had suffered atrophic changes or scar formation during the healing process of their leproma. Their tarsus had often shrunk, functioning inadequately as the supporting structure of the free edge of the eyelid. In addition, drooping of the eyelid had become worse due to senile changes in the skin's elasticity. On the other hand, none of their ears had suffered deformity, making them a good source for the resection of cartilage to be used for implantation.

The operative procedure is as follows:

1. The procedure is performed under local anesthesia. One percent lidocaine with 1:100,000 epinephrine is injected into the area where the incision is made: the lower eyelid and both sides of the medial and lateral angle of the eye, as well as the scaphoid fossa on the corresponding ear.

2. Skin incision (Figs. 1–5): The incision at the medial and lateral palpebral angle is required to be deep enough to reach the ligaments which are tightly bound to the orbital bones (Figs. 1–4). The incision of the lower eyelid is made about 5 mm below the bottom eyelash and undermined at the depth of the tarsus; which was frequently obscure in our cases likely due to leproma,