INTERNATIONAL JOURNAL OF LEPROSY Volume 39, Number 2
Printed in the U.S.A.

Thalidomide in the Treatment of Lepra Reactions

J. Terencio de las Aguas[1]

Lepra reactions now represent the greatest difficulty in Hansenian pathology in attaining cure of patients. In the best cases they prolong reaching the desired therapeutic target substantially.

Needless to say, lepra reactions constitute the starting point of visceral damages, as well as of dysproteinemias. The mortality rate is higher among those patients who have suffered from repeated reactional phases, which either prevent sulfone treatment or limit it to minimal doses. Lepra reactions also lead to irreversible neural lesions and force patients to undergo hospitalization.

For fifteen years, in most cases, the therapy of these reactions has consisted of steroid medication. This has proved strong, effective and rapid, but has led to the serious inconveniences of additional reactional relapses, the "phenomenon of evasion" of initial doses, intolerance, and corticoid dependence. Moreover, in many cases deterioration in the illness is marked by dissemination and lack of effective scarring of lepromatous lesions.

Our experience with thalidomide began in February 1966, when we dealt with our first six cases with initial doses of 75-100 mgm. Remarkable results were obtained in five of these cases. Since then thalidomide has been used by a great number of leprosaria, and today a large experience has been gained which confirms the suitability of the drug in the treatment of leprosy in acute stages. We have compiled our experience during these four and a half years, which is based on the records of 159 patients, all suffering from lepromatosis, except for two who were afflicted with reactional tuberculoid disease.

All these cases have been divided into several groups. The largest was made up of 129 patients suffering from classic general lepra reactions, i.e., fever, neurocutaneous lesions, general symptoms, etc. The next largest group (25 cases) consisted of patients exhibiting almost continuous reactional neuritis as the only symptoms. A third group included five cases exhibiting such other monosymptomatic reactional manifestations as orchiepididymitis, iridocyclitis and pseudo-exacerbation phenomena.

[1] J. Terencio de las Aguas, M.D., Director, Sanatorio de Fontilles, Alicante, Spain.

GROUP I. PATIENTS EXHIBITING GENERAL LEPRA REACTION

Our experience is based on 129 patients (103 males and 26 females) including 127 with lepromatosis and two with reactional tuberculoid disease. Of this group, 75 patients exhibited only one lepra reaction, while 54 suffered several reactions. The total number of treated reactional phases was 269. The 54 patients with several reactions were distributed as shown in Table 1.

Dosage. The preparation used was that supplied by the Grünenthal Laboratory, consisting chemically of phthalylglutamic acid imide in the form of 100 mgm. tablets. Initial dosages ranged from 100 to 500 mgm. tablets. The total number of reactions encountered was 269, as noted in Table 2.

CLINICAL RESULTS

Fever. This constituted one of the most constant reactional symptoms. The time of disappearance of fever in relation to the initial doses used is shown in Table 2. The table clearly shows the rapid action of thalidomide in fever disappearance, and similar correspondence with the initial dose. In the most acute lepra reactions, showing pyrexias of 39° and 40°, doses of 300-400 mgm. were employed. In cases with fever of 38-38.5°, and limited neurocutaneous character, a dose of 100 mgm. was used. In the case of most reactions initial doses were maintained until the complete disappearance of fever, and then continued for two to five days. In lepra reactions with higher fever, i.e., 39-40° in the afternoons, initial doses of 200-400 mgm. were distributed

TABLE 1. *Distribution of lepra reactions.*

Number of patients	Lepra reactions	
	Per patient	Total
2	8	16
2	7	14
2	6	12
6	5	30
15	4	60
8	3	24
19	2	38
54		194

through the 24 hours of the day. Patients in this group exhibited the most severe cutaneous and neural manifestations. The 300 mgm. dose has been used with results similar to results with the 400 mgm. dose, even though at the latter dose fever always disappeared before ten days.

The fever curve persisted longer in patients kept on corticosteroids who had suffered from lepra reactions of "reactional status" for several years. In all of these cases full disappearance of fever required more than ten days; in some cases it required up to 23 days.

Following disappearance of fever, a slight increase in fever lasting one or two days occurred in 14 per cent of cases. But this was overcome within 24 to 48 hours by increasing the dose. The maintenance dose amounted to 100 mgm. In patients who had been carried on corticosteroid treatment, notwithstanding the absence of fever, we felt it advisable to extend thalidomide treatment for 45 to 85 days even in the absence of symptomatology.

Cutaneous lesions. Most patients (84%) exhibited nodular type of erythema and nodular hypodermic lesions; in the remaining 16 percent the cutaneous lesions were of the polymorphous erythema type. Cutaneous damage improved in 90 percent of cases within 24 to 48 hours; regression and drop in fever disappeared in a parallel manner. We have noted that within one week of treatment of the erythema nodules only typical residual pigmentation was left. During treatment in some cases, coincidentally with improvement in the reactional skin lesions, there was a small outbreak of a new element of nodular erythema. Erythema lesions of polymorphous type disappeared within four to eight days.

Neuritis. Neuritis of the cubital, median and external popliteal sciatic nerves, as well as osseous and articular neuralgias were the first to experience the beneficial effects of thalidomide. In most cases patients noted decrease in pain intensity within 24 to 48 hours. Nevertheless, it was our opinion that the reactional symptom was the one persisting longer, even after fever and cutaneous lesions disappeared. For this reason in many cases we prolonged the therapy. Also, because of the neuritis, we have found it necessary to increase the dose to 300 mgm., and in some cases even to 400 mgm. for two or three days.

General conditions. General conditions in reactional patients improved in a parallel manner. Appetite was recovered, and anxiety decreased, as well as excitation, vomit-

TABLE 2. *Disappearance of fever in relation to dose of drug.*

Number of reactions	Dose in mgm. at beginning	Disappearance of fever in days in per cent			
		1–2	3–4	5–10	Over 10
2	500				100
11	400	45.5	27.3	27.3	
128	300	40.6	32.0	20.3	7.0
101	200	57.4	25.7	11.9	5.9
27	100	70.4	22.2	9.4	

ing, insomnia, etc. As previously stated *relapses* occurred, with some reactional outbreaks, in 54 cases, but they were much less frequent than in the patients treated previously with corticosteroids, and not so lasting. The time elapsed between the first thalidomide-treated reaction and the relapse was as shown in Table 3.

TABLE 3. *Elapsed time between first thalidomide-treated reaction and relapse.*

Time interval	Number of lepra reactions
Less than 10 days	15
10–15 days	19
15–30 days	31
1– 3 months	30
3– 6 months	26
Over 9 months	6
Without intermediate period	6

One of the most significant facts we have experienced with thalidomide is that, in most cases, patients who had suffered from several reactional periods were involved. All of them had been administered, or were having, corticosteroid therapy, and, of all of them, nine were in continued lepra reaction and continued steroid treatment for two to four years. We had repeatedly attempted giving up such hormonal dependency. We had never succeeded, however, because of the "rebound" of the reactions, pain intensity, and hepatic-renal visceral lesions themselves.

Nevertheless, all these thalidomide-treated patients have given up corticoids completely, and during the years under observation, they have not had any further reaction.

In any event, it must be borne in mind that these cases were those that actually called for a longer thalidomide-based treatment, larger maintenance dose, with difficult fever-curve fall. Nevertheless, in our opinion, these actually are logical circumstances following years of uninterrupted reaction of an actual "reactional status."

It is worth mentioning here a case reported in our first essay, published in the Fontilles journal, Vol. VI, No. 5, 1966, when we were forced to discontinue medication because of probable intolerance to the drug, which was noted in those patients longer affected by corticoid drugs, endocrine intolerance, obesity, Cushing-like syndrome, humped nape of the neck, hypertrichosis, etc. As these patients continued to exhibit lepra reaction, they were included in our new trials with higher dose, and, as a result, their several years'-reaction disappeared and no toxic-dermic manifestation was observed.

GROUP II. PATIENTS AFFECTED BY NEURITIS

This group included patients exhibiting neuritis, and neuralgias as a monosymptom, with such alterations in their general conditions as fever, cutaneous manifestations, etc. They have been treated for cubital neuritis and median and external popliteal sciatic nerve neuralgias and osseous and articular pain. All of them had been treated vigorously with corticosteroids, phenylbutazone and indomethacin, and relapsing neuritis was involved.

The initial dose of thalidomide was at the 300-500 mgm. level. The doses were decreased as the pain picture improved. In all cases significant improvement was observed 24 hours after commencement of treatment. Pain disappeared completely in four cases prior to the end of a week of treatment. Neuritis relapses were observed in two cases, and, as a result, it was necessary to use the drug at the 400 mgm. dosage level for two months on a daily basis. However, while some improvement was noted in two cases at a dose level of 500 mgm., some noncontinuous parenteral administration of steroid proved necessary. These are the cases that call for a higher dose (500 mgm.). The resistant cases actually call for neural liberation by surgical technologies.

GROUP III. OTHER MONOSYMPTOMATIC REACTIONAL MANIFESTATIONS

Orchi-epididymitis. Two lepromatous patients suffering from repeated orchi-

epididymitis were treated with thalidomide at the following dose levels: 300 mgm. for five days, 200 mgm. for six days, and 100 mgm. for seven days. Relief from pain was noted within the following 24 hours. The inflammatory edema decreased and the disease picture disappeared in ten days. All of these patients have remained free from relapse.

Iridocyclitis. In cases with general reaction we have already noted the tendency to severe iridocyclitis exhibited by some patients. In cases in which acute iridocyclitis was the only symptom, and relapse was frequent, thalidomide was used at a dose level of 200 mgm. for one week, and 100 mgm. for ten days. Signs of the disease disappeared rapidly.

Pseudoexacerbation. An interesting case was seen of a lepromatous patient who exhibited some nodular cutaneous lesions, grouped in bacillus-free plaques distributed in the forehead and left forearm areas. Those lesions persisted in spite of corticosteroid treatment, although they were slightly improved. Thalidomide treatment in 200 and 100 mgm. doses, however, led to total disappearance of the lesions in two months' time.

DISCUSSION

Tolerance has proved "perfect" in all cases. Sleepiness was observed in 15 per cent of cases, constipation in three per cent, and abdominal tympanism in two women.

This study, our fourth, of the use of thalidomide in the treatment of lepra reactions, has, in general, confirmed the promising results in our first experience. Initial doses at the levels of 300 and 200 mgm. have proved sufficient, and in a third of the cases the 100 mgm. dose proved enough. Results in general lepra reactions have been excellent, particularly with respect to reaction, fever, cutaneous lesions, symptoms of neuritis, etc.

In our opinion the most important clinical fact with respect to thalidomide, is its use in some patients who had been treated intensively with steroids for years, notwithstanding the patients' efforts and ours, all unsuccessful, to discontinue steroid administration. In the past, reduction of the dose of corticosteroids gave rise immediately to reactional outbreak, as well as neuritis and a bad state in general. The effectiveness of thalidomide has led to discontinuation of corticosteroid treatment in our sanatorium for the last two years. Relapses have been rare, and no immediate reaction has occurred on suspension of treatment or decrease of dose.

The rapidity of disappearance of reaction has been somewhat less than that effected by corticosteroids, particularly in the fever curve. But it is our opinion that thalidomide is superior, because of its nonhabituating character, absence of secondary reactions, and lower frequency of relapse.

As a matter of fact, the behavior of the drug has not yet been assessed precisely. We were aware of its analgesic and hypnotic behavior, which no doubt gave rise to improvement from some reactional symptoms, but disappearance of cutaneous lesions, neural build-up, and the fever curve made us think of the anti-inflammatory effect observed as the result of hypophyseal stimulation or immunosuppressive action.

There is no doubt that we are dealing with an effective drug, which is superior, with respect to patients' tolerance, to other remedies recently used in lepra reactions. Furthermore it has enabled us to eliminate hormonal dependence on steroid, which had been the rule for the past few years.

SUMMARY

After four years of experience with thalidomide in the treatment of lepra reactions, results can be summarized as follows:

Some 159 patents, all suffering from lepromatosis, except for two affected by reactional tuberculoid disease, were treated. The cases included 129 patients exhibiting general lepra reactions, 25 with reactional acute neuritis, two with orchi-epididymitis, and one with lesions of pseudoexacerbational type. Of the 129 patients with general lepra reaction, 75 had only a single reactional process, while 54 had several outbreaks.

The total number of thalidomide-treated acute reactional incidents was 269. At the beginning, doses ranged from 100 to 500 mgm. In every case the reaction treated disappeared, and efficiency and rapid action of the drug were noted with respect to different reaction symptoms, such as fever, neuralgias, and cutaneous lesions. Thalidomide also showed its effectiveness in neuritis, iridocyclitis and orchi-epididymitis.

In two cases with reactional neuritis as the only symptom, thalidomide administered in 500 mgm. daily doses actually led to improvement, but not sufficiently to overcome pain completely, and consequently surgical therapy proved necessary.

Tolerance to the drug proved excellent in 100 per cent of cases.

The length of treatment was related to the intensity and evolution of the reactional process. On the average, and in most cases, the drug was administered for a month. Initial doses were decreased in proportion to improvement from reactional symptoms.

One of the most interesting aspects of the thalidomide-based treatment, was that in a large number of the first cases patients affected by continuous lepra reactions were concerned. These showed a "reactional status" of several years' duration, in which corticoid treatment was uninterrupted and could not be replaced. However, when these patients were treated with thalidomide, they could discontinue steroids. Reactions were obviated and all these patients reacted favorably in the direction of cure.

The interesting fact may be pointed out that since we have been able to count on thalidomide no further corticosteroid treatment has been used at Fontilles. Also a decrease in reactional phases is being noted, which is attributed to far less frequency of relapses in thalidomide-treated cases.