

Thalidomide Therapy in the Lepra Reaction^{1, 2}Jacinto Convit, José M. Soto and J. Sheskin³

In earlier, initial investigations J. Sheskin of the Hadassah Hospital of Jerusalem reported that thalidomide (n-phthalimido-glutarimide) was highly effective in the treatment of lepra reaction. More recently extensive trials by the double-blind method were carried out in Venezuela as a joint investigation by the Hebrew University of Jerusalem, the Division of Sanitary Dermatology of the Ministry of Health of Venezuela, and the Central University of Venezuela. In this investigation the results of the earlier work in Israel were confirmed, and a remarkable effectiveness of the drug in the treatment of the lepromatous lepra reaction was established (⁶).

The present report deals with the direct treatment of a group of lepromatous patients with thalidomide to counteract their lepra reactions, which, in the majority of the cases, were severe and of long duration.

MATERIALS AND METHODS

A group of 24 patients with lepromatous leprosy in a reactional stage were selected for the treatment. They presented polymorphous erythemo-nodose lesions, and the reaction was severe and of long duration in 70 per cent, as a result of months and even years of steady aggravation. Treatment with corticosteroids had been frequent and of variable benefit. Secondary effects of those drugs had often been evident.

The patients were conventionally classified according to the intensity of their reactional state. By R3 we designated patients who showed profuse reactional eruptions of nodose or polymorphous erythema with intense dermalgia and edema of the extremities, pain in the joints and muscles, and severe headaches. In some patients, although not in all, there was acute neuritis. The general health of the patients was greatly lowered by fever, which rose frequently to above 39°C, vomiting, loss of appetite, and insomnia.

As R2 we classified patients with a less severe reaction, characterized by the symptoms of the R3 group, but in lesser degree, with fever not exceeding 38°C, but without prostration and with the ability to move about, although with some difficulty.

The R1 group included patients with erythemo-nodose or erythemo-polymorphous manifestations, with subfebrile temperature, with or without moderate pains, but without any notable lowering of their general health.

In the group of 24 patients selected, of whom 16 were males and eight females, 19 were classified as R3 or R2.5. In the group R3 we included two patients with acute polyneuritis who did not show the intensity of the reactional symptoms evident in the rest of the group. The age of the patients varied from 17 to 62 years, with 19 between the ages of 30 and 62. All of them were hospitalized under conditions of strict medical control.

The strictest vigilance was observed with the eight women in the group. They had been submitted to special control to eliminate all suspicion of pregnancy in view of the teratogenic properties of the drug.

Doses employed. The drug was administered in daily doses of 400 mgm. in portions of 100 mgm., every 6 hours. However, in the cases that had received treatment with

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corticosteroids during long periods the daily dose was 500 mgm. in the early stages of the experimental treatment.

In all patients a clinical observation of vital signs was made twice a day. Routine laboratory examinations were made of urine, feces, and blood, with determination of urea, glycemia, and transaminase, and repeated every two weeks.

A graphic record was kept for each patient, showing, day by day, all changes in his reactional state. When a regression was plainly evident, the dose of thalidomide was reduced to a maintenance level, which in some cases was as low as 50 mgm. daily without reappearance of the reactional syndrome. Because of the uniform response to treatment of the patients, both those who had taken corticosteroids for long periods of time, and those who had not, a diagram

was made for each group in order to show the uniformity of response graphically (Figs. 1 and 2).

RESULTS

The observations justify us in considering the results separately in patients who had never been treated with corticosteroids in comparison with those who had been treated with those drugs for long periods previous to treatment with thalidomide. The initial reaction to the latter was quite different in the two groups.

1. Patients without previous treatment with corticosteroids. In this group the daily administration of 400 mgm. of thalidomide reduced the temperature from its previous febrile condition to normal in the course of 48 hours, and attenuated the reactional syndrome greatly during the

TABLE 1. *Treatment with thalidomide. Lepromatous patients in the reactional state.*

Patient	Age	Sex	Intensity	Reaction of long duration	Treatment	
					Previous steroid	Duration with thalidomide (months)
J. R.	17	M	R3	yes	yes	1
M. M.	30	F	R3	no	yes	5
A. M.	55	M	R3	yes	yes	3.5
A. B.	32	M	R3	yes	yes	8
J. C.	43	M	R2.5	no	no	8
M. G.	36	F	R3	yes	yes	7.5
J. T.	43	F	R1	no	no	7.5
R. V.	57	M	R2.5	no	no	2
G. A.	33	M	R2	yes	yes	4
F. C.	23	M	R2.5	yes	yes	4
J. A.	46	M	R3	yes	yes	1.5
J. U.	45	M	R2.5	yes	yes	1.5
J. R.	30	M	R2.5	no	yes	3.5
D. Ch.	62	M	R2	no	no	3.5
M. Ch.	40	F	R3	yes	yes	2.5
E. R.	39	M	R3	yes	no	3.5
U. M.	18	F	R2.5	yes	yes	3
M. G.	30	F	R3	yes	yes	2
J. M.	52	M	R3	yes	yes	1
D. F.	47	M	R3	yes	yes	1
H. P.	53	F	R2	no	yes	1
R. P.	21	M	R2.5	yes	yes	2.5
M. O.	33	F	R1	no	no	1
J. B.	40	M	R3	yes	yes	1

same period. The patients could sleep and eat, and get out of the bed in which they had been lying prostrate before. In the course of four to five days all symptoms of the reactional state had disappeared (Fig. 1).

2. Patients treated with corticosteroids for long periods. When treatment with thalidomide was started, corticosteroid treatment was suspended. In these patients there was a marked aggravation of their reactional state during the first 48 hours of thalidomide treatment. Reactions that had been moderate previously would suddenly become intensified with the whole syndrome characteristic of the R3 degree. This, however, would regress in the course of the next seven days, but the patients required from 12-14 days of treatment before all symptoms of the reactional state disappeared. This became the rule in all patients previously treated with corticosteroids.

In contrast with the patients who had never received corticosteroids, this group required a total of 6-7 gm. of thalidomide before a complete remission of the reactional state was attained. As a matter of fact, they received daily doses of 500 mgm. of the drug during the early stage of the treatment.

In Figure 2 we have shown the typical evolution of the reaction of a patient previ-

ously treated with corticosteroids. Special mention must be made of three reactional cases. Of these, two were characterized by severe, acute polyneuritis. When thalidomide was administered, the two polyneuritic cases responded with remarkable lessening of the pain after the first 48 hours and complete remission of the reactional syndrome between the fourth and fifth day. By the end of two weeks the enlargement of the ulnar nerves had been reduced considerably. In a case of acute iritis the evolution was similar, with notable improvement after the first 48 hours, and complete remission of symptoms in four to five days. In all three cases a maintenance dose of 50 mgm. daily was established gradually under complete control after the disappearance of the reactional syndrome.

In the study of laboratory data it was observed that the erythrocyte sedimentation rate was not significantly affected by the treatment. The contrary was the case with the leucocytosis that had been observed in a number of cases. In these the leucocyte count became normal after one to two weeks of treatment.

In the otherwise spectacular effect of thalidomide in counteracting the lepra reaction, there was one exception. It was a case of a lymphopathic reaction with high fever and with extensive, generalized adenopathy, which showed no improve-

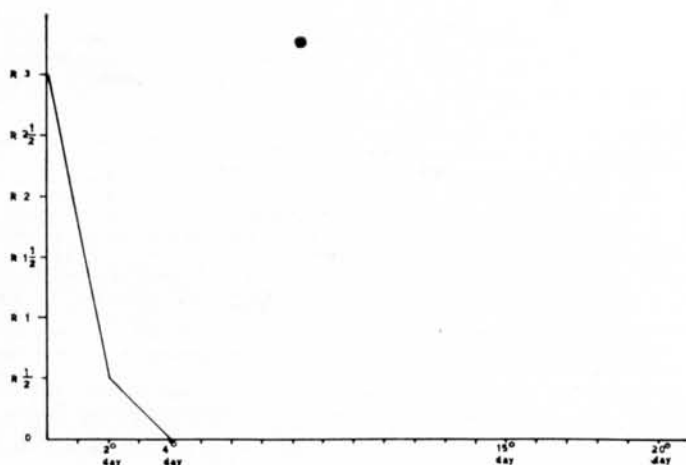


FIG. 1. Patient without previous treatment with corticosteroids.

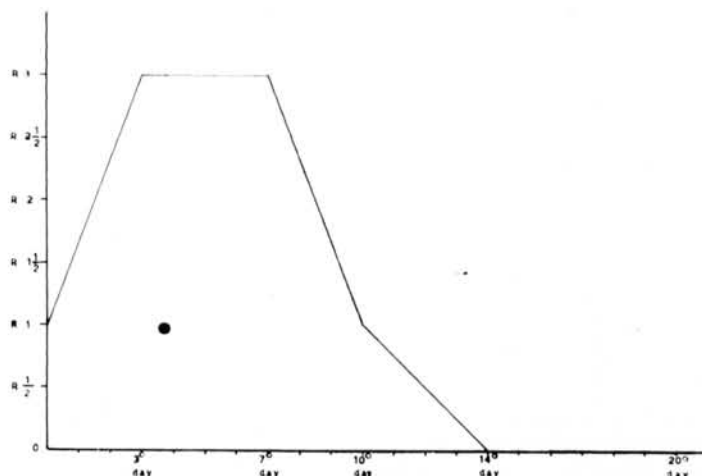


FIG. 2. Patient with previous treatment with corticosteroids

ment after two weeks, in spite of the fact that the patient had never been treated with corticosteroids.

DISCUSSION

The rapid effect of thalidomide in severe cases of reaction in lepromatous leprosy appears to be sufficient reason for us to give it foremost place among the antireactional drugs that have been used thus far. It appears very much better than the corticosteroids and it does not give the unfavorable side effects of the latter. Its greatest drawback is, naturally, its teratogenic activity, which makes it necessary to hospitalize the patients under treatment, and to keep the women of reproductive age under constant strict control. The possibility of using the drug in ambulatory patients should be restricted to males alone, and would depend on the eventual availability of an injectable "depot" preparation.

There is need for an investigation of the possibility of using thalidomide jointly with sulfone therapy in patients subject to recurrent lepra reactions from DDS.

We have already observed that patients who formerly did not tolerate even a minimal dose of DDS will tolerate up to 200 mgm. daily while receiving thalidomide. The increase in tolerance to DDS was observed even with the maintenance dose of 50 mgm. of thalidomide daily.

Another fact worth mentioning is the remarkable tolerance of patients to thal-

idomide. The only inconvenience that we have observed so far has been some constipation when the largest doses were given. It ceased when the daily dose was reduced to 200 mgm. In some cases there has been some edema of the distal parts of hands and feet, but that symptom also disappeared when the dose was reduced.

In five of our patients who had been treated continuously for five months we could find no symptoms of toxicity, clinically or by laboratory tests.

In some patients reactional manifestations have reappeared when the daily dose was lowered, but here again the syndrome disappeared spontaneously.

When treatment was discontinued after several months, some patients suffered a relapse, with symptoms as severe as those of their initial reaction, but they responded promptly to renewed treatment with thalidomide.

In view of the facts that thalidomide is split up into a dozen metabolites in the human organism (^{1,2}), and that some of these are teratogenic while others are not, it would be interesting to investigate the possibility that some of the nonteratogenic metabolites might have antireactional activity in leprosy.

There is need for an explanation of the longer time necessary for thalidomide to take effect in patients previously treated with corticosteroids, as compared with untreated reactional cases. Perhaps the corti-

costeroids suppress the activity of the adrenal cortex temporarily in one or more of its phases, and a certain time-lapse may be necessary before that activity is resumed and returns to normal.

SUMMARY

In a previous investigation by the double-blind method it was shown that thalidomide is highly effective in suppressing the lepra reaction. We have now used the drug as a regular therapeutic agent in the treatment of 24 lepromatous patients in reactional states of various degrees, although 70 per cent of them were cases of long duration in which sulfone treatment had been suspended to prevent further aggravation of the reaction.

The administration of thalidomide in doses of 400 mgm. daily to patients who had not been treated previously with corticosteroids, restored body temperatures to normal within 48 hours and brought about a complete remission of the reactional syndrome in four to five days.

The time necessary for the drug to bring the reaction under control was much longer when it was administered to patients who had been treated with corticosteroids for long periods. When that treatment was suspended with the commencement of thalidomide therapy, there was a recrudescence of the reactional state and the treatment had to be continued with doses of up to 500 mgm. daily for two weeks before the symptoms subsided and disappeared.

Cases of acute polyneuritis incident to the reactional state were also controlled rapidly and completely under treatment with thalidomide, and the same was observed in a case of reactional iritis.

After the disappearance of the reactional syndrome the daily doses of the drug were reduced gradually to a maintenance dose of 50 mgm. The administration of the drug, even on a maintenance level, enabled resumption of DDS treatment in cases that were formerly intolerant to sulfones. To all appearances the problem of antileprosy therapy in cases subject to frequent reactions had been solved.

The secondary effects of the drug were slight. At the higher doses there was some

constipation, which ceased when the dose was reduced to 200 mgm. daily. Under prolonged treatment edema of the distal extremities was also observed as a temporary side effect.

In view of the teratogenic activity of thalidomide patients should be hospitalized under strict control.

RESUMEN

En una investigación previa mediante el método doble-ciego se demostró que la thalidomide es altamente efectiva en la supresión de la reacción leprótica. Nosotros hemos usado ahora la droga como un agente terapéutico regular en el tratamiento de 24 enfermos lepromatosos en estados reaccionales de diversa intensidad, aunque 70 por ciento de ellos eran casos de larga duración, en los cuales el tratamiento con sulfona había sido suspendido para prevenir una mayor gravedad de la reacción.

La administración de thalidomide en dosis de 400 mgm. diariamente a pacientes que no habían sido tratados previamente con corticosteroides, devolvió la temperatura del cuerpo a nivel normal dentro de las 48 horas y produjo una remisión completa del síndrome reaccional en cuatro a cinco días.

El tiempo que la droga necesitó para controlar el proceso reaccional fué mas largo cuando fué administrada a pacientes que habían sido tratados con corticosteroides por largos períodos. Cuando este tratamiento fué suspendido al comienzo de la terapia con thalidomide, hubo una recrudescencia del estado reaccional y el tratamiento tuvo que ser continuado con dosis hasta de 500 mgm. diarios por dos semanas antes que los síntomas se atenuaran y desaparecieran.

Casos de polyneuritis aguda coincidentes con el estado reaccional fueron también controlados rápida y completamente con el tratamiento con thalidomide, y lo mismo se observó en un caso de iritis reaccional.

Después del desaparecimiento del síndrome reaccional la dosis diaria de la droga fué reducida gradualmente a una dosis de mantención de 50 mgm. La administración de la droga, aún en un nivel de mantención, permitió reanudar el tratamiento con DDS en casos que anteriormente mostraron intolerancia a las sulfonas. Bajo todas las apariencias el problema de tratamiento antileproso en casos sujetos a reacciones frecuentes había sido resuelto.

Los efectos secundarios de la droga fueron menores. Con dosis mas altas hubo constipación, que cesó cuando la dosis fué reducida a 200 mgm. diarios. Bajo tratamiento prolongado se observó edema de las zonas distales de las extremidades como un efecto temporal.

En vista de la actividad teratogénica de la thalidomide, los enfermos deberian ser hospitalizados y permanecer bajo estricto control.

RÉSUMÉ

Au cours d'une étude antérieure, menée par la méthode du double incognito, on a montré que la thalidomide est fort efficace pour supprimer la réaction lépreuse. Jusqu'à présent, nous avons utilisé ce médicament comme agent thérapeutique de routine dans le traitement de 24 malades lépromateux souffrant d'état réactionnel de gravité diverse. Dans 70 pour cent des cas, il s'agissait de malades atteints d'une affection de longue durée, chez lesquels le traitement sulfoné avait été interrompu afin de prévenir une aggravation encore plus forte de la réaction.

L'administration de thalidomide, à des doses de 400 mgm. par jour, chez des malades qui n'avaient pas été traités antérieurement par des cortico-stéroïdes, a ramené la température corporelle à la normale endéans les 48 heures et a entraîné une disparition presque complète du syndrome réactionnel en 4 ou 5 jours.

L'intervalle de temps nécessaire pour que le médicament réussisse à contrôler la réaction a été beaucoup plus long lorsqu'il était administré à des malades ayant été antérieurement traités par des cortico-stéroïdes pour de longues périodes. Lorsque ce traitement était interrompu au moment où la thérapeutique par la thalidomide était instituée, on assistait à une recrudescence de l'état réactionnel; pour que les symptômes s'effacent et disparaissent, il fallait continuer le traitement avec des doses allant jusqu'à 500 mgm. par jour pendant deux semaines.

Les épisodes de polynévrite aiguë accompagnant l'état réactionnel étaient également contrôlés rapidement et complètement grâce

au traitement par la thalidomide; il en a été de même pour un cas d'iritis réactionnel.

Après la disparition du syndrome réactionnel, les doses journalières du médicament ont été progressivement ramenées à une dose de maintien de 50 mgm. L'administration du médicament, même à cette dose de maintien, a permis la reprise du traitement par le DDS chez des malades qui étaient auparavant intolérants aux sulfones. Il a vraiment paru que le problème de la thérapeutique antilépreuse chez des malades sujets à des réactions fréquentes a été résolu.

Les effets secondaires du médicament étaient peu importants. Aux doses les plus élevées, on a noté un peu de constipation, qui cessait lorsque la dose était ramenée à 200 mgm. par jour. Au cours de traitements prolongés, de l'œdème des extrémités distales a également été observé de manière temporaire.

Par suite de l'effet tératogénique de la thalidomide, les malades doivent être hospitalisés sous surveillance médicale étroite.

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