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THALIDOMIDE IN THE TREATMENT OF CHRONIC DISCOID LUPUS ERYTHEMATOSUS

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Abstract. Renewed attention has been given to thalidomide as a useful drug for treating certain diseases, e.g. lupus erythematosus. The favourable results obtained in 5 patients suffering from chronic discoid lupus erythematosus, selected for the severity of their lesions and non-responsiveness to chloroquine, are reported. In addition, a review of the pharmacological properties of thalidomide is given.

Key words: Lupus erythematosus, chronic discoid; Thalidomide

Since the ban on thalidomide in 1961 due to its teratogenicity, new indications for its use have been mentioned in the literature. In 1965 Sheskin (17) first reported spectacular results in the treatment of leprosy reactions (erythema nodosum type) which have subsequently been confirmed by many others. More recently, in 1975, Barba-Rubio & Gonzalez Franco (1) showed that thalidomide is a useful drug for treating chronic discoid lupus erythematosus (CDLE). Nearly all patients were cured or improved appreciably. In 1979 Belaich et al. (2) demonstrated its spectacular success in a patient in whom antimalarial treatment had to be discontinued. A similar patient was presented by Civatte (4) who showed impressive regression of CDLE after 4 weeks of therapy. Equally impressive results obtained in larger groups of patients were reported by Spanish, West-German and French workers (8, 12, 16).

CASE REPORTS

The clinical diagnosis of CDLE was confirmed in all patients by histopathological examination and immunological investigation using immunofluorescence techniques.

Selection of the 5 patients admitted to the trial with thalidomide was based upon two criteria: exacerbation of existing skin lesions and non-responsiveness to chloroquine treatment. Pregnancy in the 3 female patients concerned was impossible because of sterilization, oral contraconception, or advanced age.

Case 1

A 35-year-old woman suffering from CDLE for 11 years, localized on the cheeks, the nose and the extensor sides of the extremities. Repeated episodes later included arthralgia, with elevated ESR and presence of rheumatoid factor. Positive ANA, but negative LE cell test, absent dsDNA antibody and normal amounts of C_3 and C_4. In uninvolved skin, no IgG deposits were present in the basement membrane. Initially, treatment consisted of chloroquine, since 1978 combined with oral prednisone.

Recrudescense of lesions despite this therapy led to additional treatment with thalidomide (three times 50 mg daily). Upon clinical improvement after 2 weeks, chloroquine and prednisone were discontinued. After 2 months the dosage of thalidomide was lowered to 100 mg daily, as the extension and infiltration of skin lesions was markedly decreased. After 12 months of continued treatment no exacerbation was seen.

Case 2

A 35-year-old woman with recurring disseminated lesions of CDLE for 6 years. Laboratory investigations yielded positive ANA, incidentally raised ESR and rheumatoid factor, negative LE cell test, absent dsDNA-antibody and normal amounts of C_3 and C_4. In uninvolved skin, slight IgG deposition at the basement membrane was once seen, but repeated internal examination failed to prove the presence of systemic disease.

Initial treatment consisted of chloroquine and local steroid application. Two years ago treatment was stopped because complete remission of lesions. One year ago, in summer, a generalized exacerbation of previously existing lesions was seen, which did not respond to high dosage chloroquine treatment. Worsening of the skin lesions (Fig. 1) led to discontinuation of chloroquine and to institution of thalidomide treatment (3×100 mg daily). After 2 weeks, clinical improvement (Fig. 2) led to halving of the dosage. After 6 weeks, of appreciably reduced skin lesions, leaving residual pigmentation only, all treatment was stopped.

A slight recurrence last summer was cured after 2 weeks of reinstituted thalidomide treatment. All treatment was stopped after 4 weeks. At the time of completion of this report (after 3 months) no further relapse has been seen.

Case 3

CDLE in a woman of 61 years, a patient for 30 years, was first localized on the face, later extending to the scalp and the backs of the hands and in particular of index fingers.

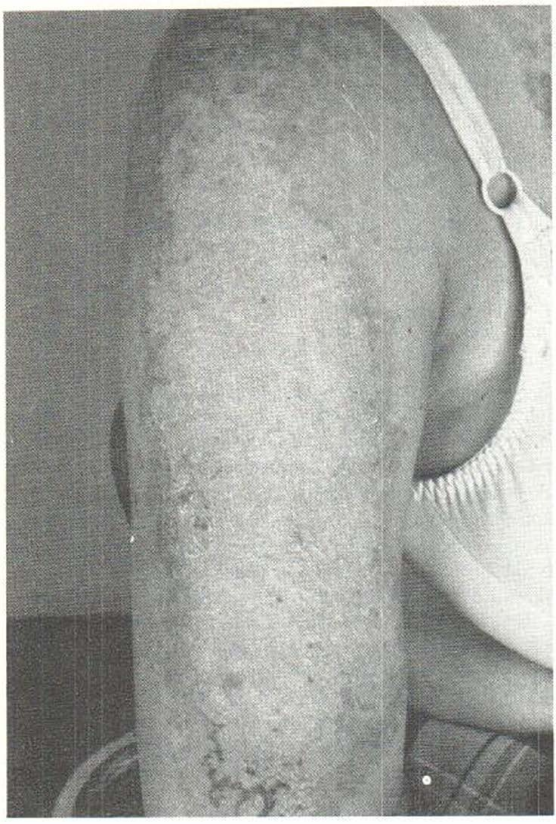

Fig. 1. Case II. Upper arm at start of treatment.

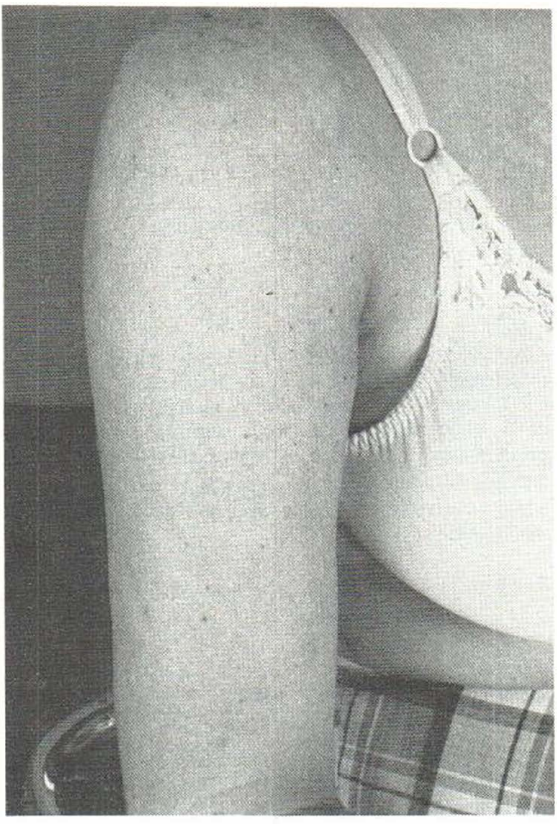

Fig. 2. Case II. Upper arm after 2 weeks of treatment.

Bismuth and gold injections preceded antimalarial treatment.

Chloroquine treatment instituted later increasingly failed to cure. As a contracture of the right index finger developed, amputation had to be carried out to improve the functional capacity of the right hand. Laboratory examination carried out in recent years incidentally showed positive ANA, but LE cell test, dsDNA antibody were negative and deposits of IgG in normal skin were absent.

Last year exacerbation of skin lesions occurred on face and hands. In particular the painful lesions on the left index finger caused concern for fear of subsequent amputation of this finger. At this time thalidomide (3×100 mg daily) was administered and all previous treatment discontinued. After 2–3 weeks, skin lesions improved, while the pain in the index finger had completely disappeared. After 10 weeks the extension and infiltration of lesions was markedly decreased, and after gradually lowering the dosage of thalidomide all treatment was stopped after 6 months. Up to date, no reappearence of the lesions has been observed.

Case 4

A 56-year-old man with CDLE for 7 years, localized on face, hands and at times spreading to neck, shoulders and legs, has since been treated with chloroquine.

Laboratory examination once only yielded positive ANA and rheumatoid factor, but the LE cell test proved negative. Uninvolved skin did not show IgG deposits at the basal membrane.

As infiltrated skin lesions on face and hands no longer responded to chloroquine and as stiffness and pain in the fingers became prominent, thalidomide therapy (200 mg daily) was given. Two months later therapy was stopped when skin lesions showed only macules, with slight scaling and pain, and stiffness had disappeared.

Three weeks after discontinuing treatment a slight relapse of skin and joint complaints necessitated reintroduction of thalidomide. With a maintenance dose of 50 mg daily, a return to normal has occurred in 6 months.

Case 5

A 48-year-old man afflicted with CDLE for 9 years, localized on scalp and face, with extensive scarring and alopecia. Laboratory examination recently yielded negative ANA. Uninvolved skin did not show IgG deposits at the basal membrane.

The patient was presented for advice by a skin specialist because of non-responsiveness to chloroquine and recrudescence of all lesions. Particularly on the scalp, large areas of alopecia were seen, bordered by scaling, infiltrated and erythematous lesions. Thalidomide therapy (100 mg daily) was started in addition to chloroquine. The

latter was discontinued after one month because marked improvement was seen. One month later the dosage of thalidomide was halved in view of the disappearance of all infiltration and scaling. Therapy was stopped after 2 months. Slight reappearance of lesions after 1 month could initially be coped with by locally applied steroid therapy.

Recent recrudescence of the periphery of the scalp lesions led to reinstitution of thalidomide treatment (100 mg daily) with prompt disappearance of clinical lesions within 3 weeks. The patient has since been kept on maintenance therapy with 50 mg thalidomide daily, without showing active disease.

PHARMACOLOGY

Thalidomide, α-phthalimidoglutarimide ($C_{13}H_{10}O_4N_2$) a non-barbiturate hypnotic, consisting of a mixture of the D and L form, after oral intake is equally distributed in the body, with slightly increased presence in skin and kidneys, but little fixation in the liver. Metabolic substances produced by hydrolysis consist of D/L-glutamine, D/L isoglutamine, D/L-glutaminic acid and phthalic acid. Excretion of metabolites takes place mainly via the kidneys, while a small proportion is excreted via the bile. The half-life of thalidomide in test animals is 3–4 hours; in man this time is probably longer.

Thalidomide, though a hypnotic drug, did not produce pathological effects at the microscopical level in the nervous system of test animals, irrespective of the dosage (18).

The mode of action of thalidomide, including its teratogenicity, is still far from clear. Thalidomide, when added to cell cultures, produced chromosome anomalies (9). D- and L-thalidomide and some of its metabolites in vitro produced inhibition of lymphocyte proliferation (13). The prolonged survival time of skin transplants in mice treated with thalidomide and the decrease in number of immunoblasts in their regional lymph nodes, led to the assumption of its immunosuppressive properties (19). Different results were obtained by other authors (3, 5, 6). Dukor & Dietrich (5) found only a marginal prolongation of the survival time of skin transplants in an experiment in which both donors and receivers were treated with thalidomide. Neither Floersheim (6) using mice treated with different dosage schedules, nor Bore & Scothorne (3) found any difference in survival time of skin transplants, the latter comparing results in treated and non-treated rabbits. Sagher et al. (14) were unable to show any influence of thalidomide on the complement system, nor could any effect upon endogenous corticosteroidproduction be proved. Salaün (15) considered the possibility of thalidomide interfering with the metabolism of vitamin B. Klüken & Ventz (7) suggested a stabilizing effect on lysosome membranes similar to that produced by corticosteroids.

Teratogenicity is the main side effect produced by thalidomide. It easily passes the placental barrier and even a single small dose administered in pregnancy is capable of producing its teratogenic effect. Apparently this effect is species-related, as malformation is more frequently seen in the offspring of rabbits, less in mice and seldom in rats. An adverse effect upon spermatogenesis is still uncertain (11). Less important side effects are confined to the nervous system, the skin and mucous membranes and the gastro-intestinal tract. The presenting signs can be listed as follows: drowsiness, dizziness, convulsions and paraesthesias, dry skin, erythema, facial edema, urticaria, nausea, obstipation and increase in appetite and weight. Polyneuropathy may evolve after prolonged intake of the drug (6–9 months) which is thought to be irreversible if the drug is not stopped immediately. Only once (16) has relative leukopenia been mentioned as the sole hematologic side effect seen. However, side effects rarely seem to cause discontinuation of treatment (1, 10, 16, 17).

COMMENT

Marked results of treatment with thalidomide in all 5 patients with exacerbating lesions under chloroquine treatment were obtained.

First signs of clinical response were always seen within 2 weeks. During the mean observation time after the start of treatment (one year in cases 1–3, 10 months in case 4 and 7 months in case 5) in 3 cases reappearance of lesions was seen in the summertime, while the drug had been discontinued. The starting dosage was 100–300 mg daily, which was decreased upon signs of improvement, maintaining a level of 50 mg daily. In 2 patients therapy could be stopped without subsequent reappearance of lesions.

Side effects were encountered in only 2 patients (drowsiness, dizziness, increase of weight and amenorrhoea) but did not necessitate the stopping of treatment. Only in one patient (case 1) was a marked change in laboratory data seen—the elevated ESR fell substantially. Finally the need is stressed for maximum safety in avoiding pregnancy in women at risk (medication to be started after menses, under strict contraceptive measures, and monthly pregnancy testing).

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