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A Treatment of Corticosteroid-Dependent Lepromatous Patients in Persistent Erythema Nodosum Leprosum

A Clinical Evaluation of G.30320 (B663)

F. M. J. H. IMKAMP, O.D.S., M.B. (UTRECHT), L.A.H. (DUBLIN)
Medical Superintendent, Liteta Leprosarium, Zambia

Attention to the anti-inflammatory effect of B663 was first drawn by Browne[3 4]. In 2 patients receiving 600 mgm. B663 daily, Williams *et al.*[10] observed that the drug apparently controlled the signs of erythema nodosum leprosum (ENL).

Pettit[7] on the other hand, reported that B663 in a dosage of 100 mgm. daily had no dramatic effect in patients with very severe ENL (grades 3 and 4). He did, however, show that B663 had an anti-bacterial action in leprosy, thus confirming the early reports of Browne and Hogerzeil[5], Barry and Conalty[2] and Pettit *et al.*[8]

It is of great importance to find a drug that is effective in the control of ENL, which, when severe, is most distressing to the patient and very difficult to treat. Jopling[6] advocates the use of ACTH (cortico-trophin) or corticosteroids, with due regard to their limitations and serious side effects.

Because of the conflicting reports concerning the value of B663 in patients suffering from lepromatous leprosy with severe and long-standing ENL, we decided to put the drug to the test.

THE PATIENTS

Eighteen lepromatous patients (10 of them males) were selected for study.

Their ages ranged from 20-54 years when the B663 treatment was begun. In all of them the lepromin test (Mitsuda) was completely negative. All had suffered long periods of chronic severe ENL, classified 3+ to 4+ (Waters[9]), before the trial started. They were corticosteroid dependent, and some could be considered as being addicted to the drug. They had received corticosteroids continuously for from 9 months to 4 years and 5 months, the average being 2 years 7 months. All the patients had previously been receiving anti-leprosy drugs, 16 of them DDS; all had also received thiambutosine, and 13 had had isoniazid. A number of drugs had been used on occasion, including thiacetazone, streptomycin, sulphorthormidine and ditophal. Each patient had his own pattern of ENL which recurred when attempts were made to reduce—even slightly—the dose of corticosteroids. All were bedridden, wasted and in very poor condition.

METHOD OF INVESTIGATION AND FOLLOW-UP

Chest X-ray examination was made of all patients at the beginning of the trial to exclude pulmonary tuberculosis. Regular urine tests were carried out for albumin, sugar and urobilinogen; haemoglobin levels and the white cell count were estimated every 2 months during the period of the trial; the differential white cell count was done at the beginning of the trial and after 12 months.

LEPROSY INVESTIGATION

Smears (Wade's technique) were taken from 7 sites every 2 months for calculation of the bacterial index (B.I.), and the morphological index (M.I.).

TABLE I

Patient Number and Sex	Age when B663 started years	Date of Admission to Liteta	Length of time on Prednisolone for ENL and maximum dose	Date when B663 started and daily dose	Length of time on Prednisolone or ACTH after B663 started	Time to control ENL	Time to suppress ENL	Effect of increased dose of B663 on relapse and max. daily dosage	Comments
1 Male	41	6.61	4 years 3 months 50 mgm.	8.66 200 mgm. 1/12 100 mgm. 1/52 200 mgm. 1/52 then 100 mgm.	4 months	2 months	4 months	Very good 200 mgm.	Continuous ENL since 1962, extensive nodulation with breakdown, lymphadenopathy, abscess, fever, generalised neuritis, systemic upset together with large bed sores and emaciation, orchitis, insomnia. Now employed as full-time clerical officer.
2 Male	32	8.64	4 years 1 month 50 mgm.	8.66 100 mgm.	None	Few days	Few days	No relapse	Generalised nodular eruption, malaise, high fever, punched out ulceration on arms and legs. August, 1967, lepromata resolved, ulcers closed. Now leading normal life in leprosarium.
3 Male	28	1.62	3 years 6 months 50 mgm.	7.66 100 mgm. 6/12 200 mgm. 2/52 then 100 mgm.	None	Few days	6½ months	Very good 200 mgm.	Large painful nodules and ulnar neuritis. Now working in leprosarium as ward attendant.
4 Male	31	8.62	2 years 10 months 50 mgm.	2.66 100 mgm.	None	1 week	2 weeks	No relapse	Initially extremely ill with severe deep bone pain, painful intracutaneous nodules, ulnar neuritis. Now leading normal life in leprosarium.
5 Male	30	2.63	2 years 10 months 50 mgm.	7.66 100 mgm. 2/12 200 mgm. 2/52 then 100 mgm.	6 weeks	1 month	2 months	Very good 200 mgm.	Multiple painful nodules with extensive ulceration, ulnar neuritis, attacks of orchitis. Now working as bricklayer in leprosarium.
6 Male	35	4.64	2 years 2 months 50 mgm.	9.66 100 mgm.	None	Few days	Few days	No relapse	Extensive painful nodules and neuritis, arthritis, general malaise, deep bone pain and insomnia. Now leading normal life in leprosarium.
7 Male	44	3.64	2 years 2 months 50 mgm.	6.66 100 mgm. 2/12 200 mgm. 10 days 300 mgm. 11 days 200 mgm. 6/52 then 100 mgm.	7 weeks	10 weeks	3 months	Very good 300 mgm.	Generalised swelling and painful nodules, iridocyclitis, median and ulnar neuritis, oedema of legs, feet, deep pain, fever. Now leading normal life in leprosarium.
8 Male	44	7.64	2 years 1 month 50 mgm.	8.66 100 mgm.	8 days	2 weeks	1 month	No relapse	Generalised nodular eruption, left ulnar neuritis, lymphadenopathy, orchitis, fever. Now leading normal life in leprosarium.
9 Male	54	5.64	1 year 9 months 50 mgm.	3.66 100 mgm. 10/12 200 mgm. 3/52 then 100 mgm.	3 months. Stopped 3/52 Short course 3/52	6 months	10 months	Very good 200 mgm.	Painful extensive lesions with ulcerations, epididymitis, neuritis, recurrent fever, extensive weight loss. Now employed as assistant store keeper in leprosarium.
10 Male	25	9.64	10 months 50 mgm.	7.66 100 mgm. 200 mgm. 300 mgm. 400 mgm. varied Finally 100mgm.	1 month Stopped 2/52 Short course 2/52	1 month	1 year	Excellent 400 mgm.	Very severe neuritie pain in ulnar and median nerves, ulcerated skin lesions and fever. Now ambulant patient in wards requiring daily physiotherapy for contractures of hands.
11 Female	43	10.61	4 years 5 months 50 mgm.	6.66 100 mgm.	1 week	Few days	1 week	No relapse	Extensive panniculitis and persistent, painful lepromata with pain in arms and legs and fever. Now performing normal domestic duties in leprosarium.
12 Female	26	6.61	4 years 2 months 75 mgm.	8.66 100 mgm. 2/52 200 mgm. 10/52 then 100 mgm.	1 week	1 week	3 months	Very good 200 mgm.	Extensive nodular lesions, swelling of hands and feet, fever, general malaise. Now performing normal domestic duties in leprosarium.
13 Female	31	8.61	3 years 6 months 50 mgm.	9.65 100 mgm. 11/12 200 mgm. 7/52 then 100 mgm.	11 months*	3 weeks	2 months	Very good 200 mgm.	*(For the first 11 months no attempt was made to withdraw steroids completely, as this was before the trial started.) Extensive painful lesions with fever, headache and all peripheral nerves painful. Arthritic ankles and knees, swelling of hands and feet, general malaise. Now performing normal domestic tasks in leprosarium.
14 Female	20	12.62	2 years 6 months 50 mgm.	8.66 100 mgm. 6/52 200 mgm. 1/52 300 mgm. 6/52 200 mgm. 2/52 then 100 mgm.	6-day course 9 days after starting B663	12 weeks	15 weeks	Very good 300 mgm.	Extensive painful nodules, laryngeal oedema, polyarthritis, neuritis, lymphadenopathy, fever. Now performing usual domestic duties in leprosarium.

TABLE I (cont.)

Patient Number and Sex	Age when B663 started years	Date of Admission to Liteta	Length of time on Prednisolone for ENL and maximum dose	Date when B663 started and daily dose	Length of time on Prednisolone or ACTH after B663 started	Time to control ENL	Time to suppress ENL	Effect of increased dose of B663 on relapse and max. daily dosage	Comments
15 Female	32	10.63	1 year 10 months 50 mgm.	9.66 100 mgm. 4/12 200 mgm. 1/12 then 100 mgm.	None	Few days	5 months	Very good 200 mgm.	Extensive nodular painful eruption, ulnar and popliteal neuritis. General body pain. Discharged to leprosarium and became pregnant in August, 1967.
16 Female	42	11.63	1 year 6 months 50 mgm.	7.66 100 mgm. 2/12 200 mgm. 2/12 100 mgm. 5/12 200 mgm. 4/12 300 mgm. maintenance dose	3 days	2 months	13 months	Good 300 mgm. maintenance	Continuous nodular eruption of large areas, fever, insomnia, extensive neuritis. Now performing normal domestic duties in leprosarium.
17 Female	40	4.64	1 year 5 months 50 mgm.	7.66 100 mgm. 3/12 200 mgm. 1/52 then 100 mgm.	None	2 months	3½ months	Very good 200 mgm.	Repeated attacks of generalised nodular eruptions, arthritis pains, bone pain in arms and legs. Now performing normal domestic duties in leprosarium.
18 Female	36	8.66	9 months 50 mgm.	8.66 100 mgm.	None	Few days	Few days	No relapse	Extensive nodular eruptions with suppurating ulcers, fever, swelling of feet, neuritis. Now performing usual domestic duties in leprosarium.

Biopsies were taken at the beginning, after 3 months and then at 6-monthly intervals (except the initial biopsy from patients who were too ill even for a biopsy). These were examined and reported on by the Leprosy Study Centre, London.

ASSESSMENT OF RESPONSE

Pettit[7] used the dose of ACTH required as a measure of assessing the progress of the patients. We concur that the amount of corticosteroids withdrawn, coupled with the clinical picture and biopsy reports, provides a reasonable method of assessing the anti-inflammatory action of a drug under investigation.

ADMINISTRATION OF B663

The absorption of B663 has been said to be enhanced when administered in olive oil (Barry[1]), and Browne[4] used 5 ml. of edible oil to facilitate absorption from the intestine. However, the addition of oil is now considered unnecessary (Vischer[11]); this was a great advantage since it would have been most difficult to persuade these critically ill patients to take a dose of oil by the mouth.

In the following case histories, our personal observations started in February, 1966; the previous facts and clinical data were summarised from clinical notes made before the writer assumed the medical care of the patients in the Liteta Leprosarium.

RESULTS

Table 1 gives a summary of the clinical findings and results of treatment. All the patients had been having repeated courses of prednisolone, starting with a dose of 50 mgm. (except Patient No. 12, whose maximum dose was 75 mgm.) and gradually reducing, but in all patients reduction of prednisolone precipitated a recurrence of ENL. When B663 treatment was begun, the patients were either on a maintenance dose of prednisolone or were just completing a course.

The starting dose of B663 was 100 mgm. per day without oil (except Patient No. 1, who began with 200 mgm. daily). Corticosteroids were discontinued at once in 7 patients, and discontinued gradually in from 1-28 days in 6 patients, and in from 1-2 months in 2 patients, and over 2 months in the other patients.

In the 7 patients (Nos. 2, 3, 4, 6, 15, 17 and 18) in whom corticosteroids were discontinued at the same time as B663 was started, ENL was rapidly controlled in all patients. Three of these patients (Nos. 3, 15 and 17) had a mild recurrence, which responded rapidly to an increase in dose of B663 to 200 mgm. per day.

Of the 6 patients (Nos. 8, 10, 11, 12, 14 and 16) whose corticosteroids were continued for from 1-28 days, 4 had recurrences of ENL. These occurred within a few days of stopping the drug in 3 patients (Nos. 10, 12 and 14), and after 6 weeks in Patient No. 16. All but one (No. 10)

responded rapidly to an increase of B663 to 200 or 300 mgm. per day (without prednisolone). Patient No. 10 had severe ulnar neuritis, was emotionally unbalanced and addicted to prednisolone; he was given a 2 weeks' course of prednisolone while B663 was continued at a dose of 100 mgm. daily. Patient No. 14 was given a 6-day course of prednisolone 9 days after beginning treatment with B663. Three of this group had further recurrences of ENL (Patient No. 14 after 6 weeks, and Patients Nos. 10 and 16 at 9 months after the start of B663). All 3 responded very well to a temporary increase dose of B663 alone.

The 2 patients (Nos. 5 and 7) in whom the corticosteroids were continued for 2 months, had a recurrence of ENL within one month of stopping the drug, but responded very well to an increase of B663 alone, for a short period.

Three patients (Nos. 1, 9 and 13) continued taking corticosteroids for a long period together with B663. In Patients Nos. 1 and 9, very gradual reduction was particularly necessary in these very ill, corticosteroid dependent and emaciated patients. Patient No. 1, who started with 200 mgm. B663 daily while the dose of prednisolone was being gradually reduced, had a recurrence of ENL when the B663 daily was reduced to 100 mgm daily while he was still having 3 mgm. prednisolone daily. This recurrence was rapidly controlled when B663 was again increased to 200 mgm. daily, for one week. No further ENL occurred when the prednisolone was eventually stopped, and the dose of B663 remained at 100 mgm. daily.

In Patient No. 9, a recurrence of ENL 16 days after steroids were stopped, necessitated a further 3 weeks' course of steroids. After 4 months on 100 mgm. B663 daily alone, the patient had a further recurrence of ENL, which responded to an increase in dose of B663 200 mgm. daily for 3 weeks, and no prednisolone. The patient is now well controlled on 100 mgm. B663 daily. As this patient was already on B663 before the trial started, he was included in the study.

In Patient No. 13, no attempt was made to stop steroids when B663 was given (Sept., 1965), as this was before the trial started. Two weeks after steroids were stopped, the patient had a recurrence of ENL, which responded to an increase dose of B663, 200 mgm. daily, alone.

WEIGHT GAIN AND LOSSES

In a few patients, weight loss was observed at the beginning of the trial. This was attributed to loss of oedema following withdrawal of corticosteroids. (Patients Nos. 2, 4, 15 and 18 losing 4, 5, 3 and 10 lbs. respectively, this weight being regained in all cases, except No. 2 whose nett loss was 2 lbs.) Of far greater significance is the increase in weight of the patients who had been seriously ill and emaciated. This can only be appreciated by seeing the individual figures, shown in Table 2. Nine of the 18 patients gained more than 10 lbs., and 5 of these gained 17 lbs. or more. This was all true weight gain, since none of the patients had any sign of oedema while on B663 treatment.

TABLE 2
Weight Gains

Patient		*Patient*	
No. 1	99 lbs.	No. 11	17 lbs
No. 3	Constant	No. 12	6 lbs.
No. 5	11 lbs.	No. 13	2 lbs.
No. 6	12 lbs.	No. 14	18 lbs.
No. 7	3 lbs.	No. 16	11 lbs.
No. 8	8 lbs.	No. 17	5 lbs.
No. 9	27 lbs.	No. 18	29 lbs.
No. 10	12 lbs.		

EFFECT ON *M. leprae*

Table 3 shows the Bacteriological Index (B.I.) and the Morphological Index (M.I.) at the outset of the trial in 1966 and at the end of 1967. An earlier figure is given for Patients Nos. 4 and 9, in whom B663 was given before the trial period. No earlier figure is given for Patient No. 13, although she also began taking B663 before the trial.

In 5 patients (Nos. 2, 3, 7, 11 and 14), the initial M.I. is higher than would be expected in patients who had been on anti-leprosy treatment for a considerable time; this may suggest that although cortico-steroids control ENL, their use may in some way have affected the action of anti-leprosy drugs.

TABLE 3
B.I. and M.I. at the start of B663 to the end of 1967

Patient No.	*B.I. mid-1966*	*M.I. mid-1966*	*B.I. end 1967*	*M.I. end 1967*
1	3.1	0%	1.0	0%
2	4.7	3.8%	3.8	0%
3	4.7	15.0%	4.2	0.2%
4	31.3.66 4.2	6.4%	3.2	0%
5	2.0	0.4%	1.1	0%
6	2.7	0%	1.1	0%
7	4.2	6.2%	3.4	0.5%
8	3.8	0.1%	1.5	0%
9	29.3.66 4.8	2.0%	4.8	1.0%
10	3.8	1.7%	3.1	0%
11	4.1	3.7%	4.1	0.2%
12	4.5	0.7%	3.0	0%
13	1.8	0%	0	0%
14	4.7	4.1%	2.5	0.1%
15	4.8	1.4%	3.2	0%
16	2.4	0%	0.1	0%
17	4.1	2.1%	3.5	0.5%
18	5.0	2.5%	4.1	0.2%

The overall picture of the smears taken every 2 months during the trial, shows a fall in the B.I. in all but 2 patients. The M.I. fell in all patients. All smears were examined by the same experienced laboratory technician throughout the trial. There was no evidence of the development of resistance to B663 in any patient.

DOSAGE OF B663

In most patients, 100 mgm. per day proved an adequate maintenance dose. Twelve patients at some time required an increased dose, which controlled a recurrence of ENL. This was either 200 or 300 mgm. per day, except in one patient who needed 400 mgm. per day. The dose used depended on the response to the initial increase.

The dose was subsequently reduced to 100 mgm. per day, with complete control in all patients except one, who required a daily dose of 300 mgm. This patient's weight being 178 lbs., it is considered that the body weight may be related to the dosage required.

SIDE EFFECTS OF B663

Gastro-intestinal

Patients Nos. 1, 10 and 12 had diarrhoea. All were taking 200 mgm. per day at that time. Patient No. 1 had been on treatment for 3 weeks and Patient No. 12 for 7 weeks. In all patients, the diarrhoea cleared rapidly when treatment was stopped for a few days. Patient No. 1 had a recurrence of diarrhoea at 8 weeks while taking 100 mgm. B663 daily. After 11 months, Patient No. 10 developed diarrhoea while on 200 mgm. per day. This patient also had some vomiting when on 100 mgm. per day, early in the investigation. At that time he was suffering from considerable emotional upset and was very reluctant to take B663 and demanded corticosteroids. This probably aggravated the vomiting. He did not vomit or have diarrhoea later when on a course of increased dosage of B663, even though at one time this reached 400 mgm. per day.

Pigmentation

All patients were told at the beginning of the trial that their skin would become darker. None of the patients objected, for at that time the majority were too ill to care, and later they regarded it as a sign that the medicine was 'doing good'.

There appeared to be no difference in the density of pigmentation between those patients who have received 100 mgm. daily and those who received a higher dosage. The parts of the body exposed to light were darker than the covered parts. This was especially noticeable in the men wearing short trousers and short-sleeved shirts. Darker pigmentation in the women was seen above the neckline of the dresses and on the forearms.

Eyes

The eyes of all patients were subjected to slit-lamp examination at the end of the trial. There was no evidence of active ocular disease or abnormal pigmentation of the conjuctival or corneal epithelium. One patient showed signs of cataracts (which had been noted before the treatment with B663 had been started).

Pregnancy

One patient (No. 15) had been on treatment with B663 from September, 1966, at a daily

dose of 100 mgm., apart from one month when she received 200 mgm. per day. In November, 1967, she delivered a normal healthy female child, weighing 7 lbs. 12½ ozs. Her pregnancy was normal and there was no increase in M.I. during pregnancy. The skin of the baby was thought to be slightly darker than is usual in this part of the world.

Laboratory Results

During the trial no abnormalities were reported in the blood or urine tests performed.

Biopsies

All biopsy reports confirmed the clinical diagnosis of lepromatous leprosy—and the last report of every patient stated: no evidence of any bacillary activity.

DISCUSSION

All the 18 patients in this investigation had been on a high dosage of prednisolone for periods varying from 9 months to 4 years and 5 months, an average of 2 years and 7 months.

They had been given frequent courses of high dosage, the usual regime being to give 50 mgm. per day at the onset of acute ENL and gradually reducing till the lowest maintenance dose was attained. In all patients, repeated attempts at withdrawal had been followed by recurrence of ENL. Four patients had developed moon-face, and another had osteoporosis and collapsed vertebrae, together with bilateral posterior capsular cataracts. All the patients were seriously ill, and so addicted to prenisolone that they demanded an increased dose at the first symptoms of recurrence of ENL. The anxiety they experienced on the withdrawal of prednisolone when B663 was begun, was quite genuine, and required high dosages of tranquillisers, a situation which persisted until the patients became aware that the ENL could be controlled by B663 alone.

After cessation of steroids, the ENL in 6 patients (Nos. 2, 4, 6, 8, 11 and 18) was completely controlled by B663, 100 mgm. daily. In a further 7 patients (Nos. 1, 3, 12, 13, 15, 16 and 17) the ENL was controlled by a temporary increase of dose to 200 or 300 mgm. a day. (Patient No. 1 was still on a reducing scale of prednisolone.) None of these 13 required further courses of prednisolone.

Five patients (Nos. 5, 7, 9, 10 and 14) were given further prednisolone together with 100 mgm. B663 daily when ENL recurred in the early stages of the trial. At this time, a cautious procedure was thought to be necessary in view of the patients' serious condition. In retrospect, it seems likely that the doses of steroids had been reduced too rapidly. Later recurrences were controlled by B663 alone, at daily dosages from 200 mgm. to 400 mgm. All could be reduced again and were controlled by 100 mgm. per day.

It is important to point out that the dose necessary to control ENL or a recurrence of ENL varies from patient to patient. If all other patients had been maintained on 100 mgm. per day, in only 6 out of the 17 (Patient No. 1 started on 200 mgm. per day) would the ENL have been controlled. This different dose regime may well explain the discrepancies apparent between Pettit's[7] findings and ours.

As described previously, effective antibacterial action was attained and sustained in all patients. One patient (No. 13) showed complete resolution of all signs and symptoms of active leprosy, with complete clearance of B.I. and M.I.

Side-effects were minimal, and there were no toxic effects. Patients improved greatly in general condition, as shown by weight gain, and all are leading a normal life; a number are employed in the leprosarium. There has been no adverse effect on pregnancy or on the foetus.

SUMMARY

A series consisting of 18 lepromatous patients is reported; all had severe ENL, which was just controllable only with large doses of corticosteroids. They were all initially bedridden, severely ill and steroid-dependent. After an average period of 2 years and 7 months of corticosteroid treatment, they began treatment with G30320 (B663) at a dose of 100 mgm. per day, except Patient No. 1, who began with 200 mgm. daily. It was then possible to stop or

withdraw steroids in all patients. Six patients had no recurrence of ENL, 7 patients had some recurrences which were controlled by a temporary increase of B663. Five patients were given prednisolone together with 100 mgm. B.663 daily, for relapses early in the trial, but subsequent relapses were controlled by an increase of B663 dosage alone. Seventeen patients were ultimately controlled with a maintenance dose of 100 mgm. of B663 per day, and one patient (No. 16) required 300 mgm. per day as a maintenance dose.

Over a period of from 14-18 months, all patients showed a steady improvement in B.I. and M.I. (except for 2 whose B.I. remained stationary). The patients showed marked clinical improvement, all are now leading a normal life, and some are employed in the leprosarium.

Side-effects were minimal, and the hyperpigmentation that developed was cheerfully accepted. All patients are most enthusiastic about B663 treatment.

It is considered that this drug represents a real advance in the treatment of ENL in that it will control persistent recurrence of such a degree as otherwise to require high dosages of corticosteroids, at the same time providing active chemotherapy.

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