Lep. Rev. (1968) **39**, 1, 3-7

B663 in Lepromatous Leprosy. Effect in Erythema Nodosum Leprosum*

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B663 is a riminophenazine derivative. The antimycobacterial activity of this class of drugs was reported in 1948[1]. In 1952 a derivative of these compounds, B283, was used in the treatment of leprosy[2]. More recently B663 has been used in the treatment of murine leprosy[3 4], mouse footpad infections with *Mycobacterium leprae*[5], and in several clinical trials in human leprosy[6 7 8 9 10 11 12 13 14 15 16].

Conclusions reached concerning the riminophenazines and B663 in particular include the following: (1) the drug is effective against a number of mycobacteria[1 17], including *Mycobacterium lepraemurium*[3 4] and *Mycobacterium leprae*[5 6 7 8 9 10 11 12 13 14 15 16], (2) the drug is apparently free of serious toxic side effects in both animals[3 18] and in humans[11 13 16]. In man and animals these compounds produce reddish skin pigmentation[2 3 6 11 13 16]. The effect of B663 on erythema nodosum leprosum (ENL) reactions in lepromatous leprosy has recently been a subject of controversy. Several studies have indicated that B663 is beneficial in ENL[9 12 13]. On the other hand, Pettitt[15] has recently claimed that B663 has no effect on ENL. The present communication deals with the effect of B663 on patients with ENL reactions at the U.S. Public Health Service Hospital, Carville, La.

METHODS

Six patients with active lepromatous leprosy associated with established erythema nodosum leprosum reactions, all requiring regular corticosteroid therapy, were selected for a trial of treatment with B663. Another group of 6 patients was selected by matching with the B663 group as nearly as possible for the factors of age, sex, race, classification of leprosy, bacteriological status, duration of leprosy, current anti-leprosy treatment, duration of ENL, and severity of ENL as measured by current steroid requirements. The second group was given regular anit-leprosy treatment with intramuscular Solapsone B.P. (Sulphetrone). The clinical data are summarized in Table 1.

The dosage of B663 employed was usually 100 mg. 3 times daily by mouth, although this varied somewhat, particularly early in the study. The dosage of Solapsone was usually 0.1 ml. of the 50% aqueous solution intramuscularly per week initially, and with the dose being raised at 2-week intervals by 0.1 to 0.2 ml. per week, when feasible, until a maximum dosage of 2.0 ml. per week was achieved. The average dosages of B663 and Solphetrone for each calendar month of the study are given in Table 2.

Each patient was seen from once daily to once weekly as long as ENL reactions were present, and corticosteroids were prescribed by one of the authors (R.C.H.) in the least dosage which would prevent (1) debilitating fever, (2) ulceration of ENL, (3) reactive neuritis producing anaesthesia of the palms, soles or cornea, and (4) reactive neuritis producing any motor weakness. The corticosteroid preparations used were oral prednisone U.S.P., injectable prednisolone sodium phosphate U.S.P. (Hydeltra-

* Presented before The USPHS Clinical Society and Commissioned Officers' Association Meeting, Atlanta, Ga., May 11, 1967.

TABLE 1

CLINICAL DATA AT THE BEGINNING OF TREATMENT

SOLAPSONE GROUP Patient	Age	Sex	Race	Class	Skin Scrapings BI*	Skin Scrapings MI	Dur. of Leprosy	Anti-leprosy** Rx in 3 mo. pre. Rx	Dur. of ENL	Dur. of Cont. Steroids	Av. daily Ster. req.for 3 mo. a Rx Pred.	Av. daily Ster. req.for 3 mo. a Rx ACTH
						%	yrs.		yrs.	mo.	mg.	u
S-1	46	M	N	BL/LL	4	1	23	None	1	14	16.6	50
S-2	27	M	W	LL	4	1	1	DDS 100 mg/wk	0.25	0	0	0
S-3	47	M	W	LL	4	1	6	None	6	3	3.8	0.9
S-4	37	M	As	BL/LL	4	1	5	DDS 5 mg/wk	1	3	9.4	1.7
S-5	37	F	W	LL	4	1	11	DDS 125 mg/wk	0.17	1	4.3	1.3
S-6	25	F	As	LL	3	1	12	DDS 50 mg/wk	2	18	19.0	2.2
Mean	36.5	2 F 4 M	2 As 3 W 1 N	2 BL/LL 4 LL	3.8	1%	9.7 yrs.		1.7 yrs.	6.5 mo.	8.9 mg.	9.4 u.
B663 GROUP Patient												
						%	yrs.		yrs.	mo.	mg.	u.
B-1	23	M	N	LL	3.3	10	6	DDS 2 mg/wk	4	13	57.8	15.0
B-2	36	F	W	BL/LL	4	1	12	DDS 8 mg/wk	2	39	5.0	22.8
B-3	53	M	W	LL	4	5	11	None	1	7	15.4	4.4
B-4	32	M	W	LL	3	2	1	Su 0.25 gm/wk So 0.008 ml/wk	1	2	3.7	1.3
B-5	51	M	W	BL/LL	4	10	30	Sm 1.0 gm/wk	26	88	11.3	9.7
B-6	29	M	As	LL	3.3	1	1	Su 0.008 gm/wk	1	11	12.2	1.1
Mean	35.7	1 F 5 M	1 As 4 W 1 N	2 BL/LL 4 LL	3.6	4.8%	10.2 yrs.		5.8 yrs.	26.7 mo.	17.6 mg.	9.1 u.

*4 = numerous = hundreds of acid-fast bacilli/oil immersion field
3 = moderate = 10 to 100 AFB/o.i.f.
2 = few = fewer than 10 AFB/o.i.f.
1 = rare = fewer than 10 AFB/entire smear
0 = none found = no AFB in 50 oil immersion fields

Su = Sulfadimethoxine (Madribon(R)—Roche)
So = Solapsone B.P. (Sulphetrone)
Sm = Streptomycin
DDS = diaminodiphenyl sulfone (Dapsone)

** None of anti-leprosy treatment regularly taken. Amounts shown are average.

TABLE 2

MEAN DOSAGES OF SOLAPSONE IN ML. OF 50% AQUEOUS SOLUTION PER WEEK AND B663 IN MG. PER DAY

SOLAPSONE GROUP Patient	MONTH* 0	+1	+2	+3	+4	+5	+6	+7	+8	+9
S-1	0.15	0.25	0.5	0.9	1.3	1.5	0.9	0.8	1.0	1.0
S-2	0.05	0.1	0.3	0.5	1.1	1.6	2.0	2.0	2.0	2.0
S-3	0.05	0.2	0.35	0.8	1.1	1.45	1.6	1.6	1.9	2.0
S-4	0.05	0.1	0.1	0.03	0.1	0.1	0.2	0.2	0.2	0.2
S-5	0.07	0.5	0.4	0.6	0.6	0.8	0.8	0.4	0.4	0.25
S-6	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.35	0.4	0.6
Mean	0.08	0.23	0.31	0.51	0.73	0.94	0.95	0.89	0.98	1.01
B663 GROUP Patient										
B-1	150	167	300	300	100	200	200	—	—	—
B-2	30	300	200	250	300	300	300	300	300	300
B-3	300	300	300	300	300	300	300	300	300	300
B-4	100	200	267	300	300	300	300	300	300	300
B-5	13	250	300	300	300	300	300	300	300	300
B-6	100	200	267	150	35	100	100	100	120	200
Mean	115	236	272	267	223	250	250	260	264	280

*Note: The 0 month indicates the calendar month in which the medication was begun; +1 indicates the first full calendar month of treatment, etc.

sol(R) Merck, Sharp & Dohme), aqueous corticotropin injection (Acthar(R) Armour), and repository corticotropin injection (H. P. Acthar Gel(R) Armour). Each dose of anti-leprosy medication, i.e., B663 and Solapsone, and each dose of the corticosteroids was dispensed by hospital nursing personnel and the medication taken either orally or by injection in the presence of the nurse on duty.

From the total amount given in each calendar month, a mean daily dose of each type corticosteroid preparation was calculated for each patient, for each calendar month, from 3 months before treatment, through 9 months

TABLE 3

MEAN DAILY STEROID REQUIREMENTS IN MG. OF PREDNISONE

SOLAPSONE GROUP Patient	MONTH*												
	—3	—2	—1		+1	+2	+3	+4	+5	+6	+7	+8	+9
S-1	19.9	44.0	60.5	43.0	49.5	40.0	37.5	36.0	56.7	79.3	56.9	20.5	30.5
S-2	0	0	0	6.5	17.3	9.0	7.3	9.8	11.8	12.4	9.5	9.9	11.2
S-3	0	3.8	8.8	41.2	43.9	47.6	57.8	58.7	68.7	76.0	64.6	70.0	68.6
S-4	3.9	20.1	7.0	10.3	18.5	26.9	29.2	27.2	28.0	49.2	41.4	39.0	28.6
S-5	1.6	4.7	8.7	9.9	10.0	10.0	10.0	10.0	10.0	11.8	16.2	15.0	20.0
S-6	16.2	15.0	29.1	29.5	31.3	39.7	43.5	40.3	40.1	43.3	39.5	40.4	32.7
Mean	6.9	14.6	19.0	23.4	28.4	28.9	30.9	30.3	35.9	45.3	38.0	32.5	31.9
Mean for 3 mo. interval		13.5				29.39			37.18			34.13	
B663 GROUP Patient													
B-1	56.7	62.7	76.5	60.9	43.4	18.5	14.2	5.7	0	0	—	—	—
B-2	20.2	15.1	14.0	14.1	20.4	26.8	17.7	7.9	5.0	10.0	9.3	7.8	2.8
B-3	11.2	25.8	15.8	22.4	21.4	14.1	21.6	22.4	17.9	19.6	14.6	14.7	15.9
B-4	0	4.4	8.7	21.8	28.0	29.7	2.2	0	0	0	0	0	0
B-5	18.6	18.8	11.0	10.5	11.5	13.5	14.8	17.0	20.0	20.8	21.0	21.4	20.4
B-6	3.7	6.5	28.0	44.0	16.8	1.8	0	0	0	0	0	0	0
Mean	18.4	22.2	25.6	29.0	23.5	17.5	11.8	8.8	7.2	8.4			
Mean for 3 mo. interval		22.09				17.58			8.13				

* The calendar month in relation to the month in which treatment was started; for example, 0 month refers to month in which treatment was started, +1 indicates first full calendar month after treatment was started, etc

after treatment was started. For the purpose of comparison it was arbitrarily considered that injectable prednisolone was equivalent, milligram for milligram, to prednisone tablets taken orally, and that 40 units of corticotropin, either aqueous or repository, was equivalent to 20 mg. of prednisone by mouth.

Mean daily steroid requirements in milligrams of oral prednisone were then calculated for each calendar month and were used to indicate the severity of the ENL reaction in each patient at that particular time. Analysis of the data for statistical significance was done by means of the T-test for small samples[19].

RESULTS

The steroid requirements for each patient in relation to treatment are given in Table 3.

The severity of the ENL reactions progressivly decreased in the group treated with B663, and the ENL became progressively more severe in the Solapsone group during treatment.

In the three months before treatment was started, the Solapsone group required an average of 13.52 mg. of prednisone per day (or its equivalent), and the B663 group required an average of 22.09 mg. of prednisone. The B663 group initially, therefore, seemed to have more severe ENL than the Solapsone group. This is not statistically significant ($0.4>p>0.3$), however, and the Solapsone group can therefore be used as a control for the B663 group.

In the first 3 full calendar months of treatment, the B663 group's steroid requirements fell to 17.58 mg. of prednisone per day while the Solapsone group now required 29.39 mg. per day as an average.

In the second 3 months' period, i.e., from the fourth through the sixth months of treatment, the B663 group continued to improve and now required only 8.13 mg. of prednisone per day while the Solapsone group continued to have more severe ENL and now required an average of 37.18 mg. of prednisone per day. This difference is statistically significant ($0.01>p>0.001$).

The steroid requirements of the Solapsone group were significantly more by the fourth through sixth months of treatment than the same group's requirements before treatment was started ($0.05>p>0.02$). The B663 group's average steroid requirements by the fourth

through sixth months of treatment were less than the same group's initial requirements, but this difference is not quite statistically significant ($0.10>p>0.05$).

DISCUSSION

It has been demonstrated that B663 is an effective drug in the treatment of human leprosy[6 7 12 13 14 16 23]. Although a recent report[15] in which a smaller dosage of the drug was used, concluded the contrary, B663 in the doses employed in the present study seems beneficial in established ENL reactions in lepromatous leprosy. It is definitely superior to the parenterally administered sulfone, Solapsone, in this respect. Several authors[20 21 22] feel that Solapsone is less likely to be associated with ENL reactions than the other sulfones. It therefore follows that B663 is less likely to be associated with ENL reactions than any of the sulfones, while at the same time exerting an anti-leprosy effect comparable to that of the sulfones.

The principal drawback of B663 at present appears to be the reddish-blue skin pigmentation it produces[6 11 13 16 23]. The present indications for the use of B663 at Carville are (1) sulfone-resistant leprosy patients, and (2) established ENL reactions requiring substantial doses of corticosteroids to control. In either of these indications the advantages of B663 over currently available treatment seem to outweigh any of the presently known disadvantages such as skin pigmentation.

SUMMARY

B663 was given to 6 patients with active lepromatous leprosy and established erythema nodosum leprosum reactions, and 6 similar patients received Solapsone. B663 was associated with significantly less severe ENL than Solapsone, and Solapsone resulted in more severe ENL than no regular anti-leprosy therapy at all. B663 seems to benefit established ENL reactions *per se*, and is definitely superior to the sulfones in this respect.

ACKNOWLEDGEMENT

The authors wish to express their gratitude to Dr. W. Vischer of Geigy (S.A.) Limited for providing a supply of B663.

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