

The Malta experience. Isoprodian–rifampicin combination treatment for leprosy

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In June 1972, the Malta Leprosy Eradication Programme was started with the cooperation of the Malta Government, the financial support of the German Leprosy Relief Association and the Sovereign Military Order of the Knights of Malta, and the assistance of the Borstel Research Institute.

The basic concept was to treat all leprosy patients known at the time, as well as any subsequent newly diagnosed patients, with an antimycobacterial combination of high effectivity, for a limited period of time as determined by their individual clinical and bacteriological progress. All patients were then to be kept under regular post-treatment control for the possibility of relapse. From *in vitro* studies, as well as clinical trials previously carried out in other countries by Freerksen and co-workers, it had been established that a fixed combination was imperative.^{1,3,4} Besides being therapeutically effective, this combination had to be administered orally and be well tolerated so as to ensure high patient acceptability and compliance. The combination Isoprodian–rifampicin was found to fit these criteria and was thus employed in the programme².

Since the therapy was administered entirely orally, the programme could be carried out on an outpatient basis from the Dermatology Department of the only general hospital on the island. With this arrangement, patients could be referred to the outpatients of any department with little inconvenience to the patient. If and when necessary, they could also be admitted to the general wards of the hospital as inpatients. In order to facilitate matters for the patients and ensure further compliance, a fortnightly outpatient clinic was also held on the sister island, Gozo. In cases where patients were unable to attend the outpatient clinics for some reason, home visits were regularly carried out.

During the treatment-period patients were examined at weekly or fortnightly intervals for the initial two or three months and then on a monthly basis. Skin smears and a biopsy were taken from every patient monthly, and these were examined at the Borstel Research Institute, where homogenated as well as histological sections were performed on all biopsy material. When the necessity arose, fresh biopsy specimens were also sent to Borstel for mouse footpad

innoculation. Skin smears were also examined in Malta for reference. During the post-treatment control period, patients were initially seen on a monthly basis and then at progressively longer intervals of two, three and six months. Smears and a biopsy were taken at every visit.

Since the start of the programme a total of 247 patients have participated. Of these, 201 were registered patients known to be suffering from leprosy at the onset of the programme, and until then, had been treated with dapsone monotherapy for a variable number of years. Forty-six newly-diagnosed patients have been included in the programme since 1972.

Figure 1 shows the age and sex distribution of the patients at the time of starting multiple drug therapy (MDT). There were no patients below the age of ten, the youngest patient being a boy aged 11, while the oldest was a man of 81 years.

Figure 2 shows the patients grouped according to the type of their disease. In a number of patients with long-standing disease, precise classification was not always possible, and therefore patients with LL and BL are grouped together as lepromatous, while those with TT and BT are likewise grouped as tuberculoid. It is clear from the figure however, that the large majority of the patients (77%) were suffering from lepromatous leprosy.

Irrespective of the type of leprosy and any previous treatment, all patients were treated with the same combination of rifampicin (2 capsules \times 300 mg) and Isoprodian (2 tablets) daily for 6 days per week. Isoprodian is a fixed

Years	M	F	T
0 - 9	-	-	-
10 - 19	7	2	9
20 - 29	5	13	18
30 - 39	21	17	38
40 - 49	41	26	67
50 - 59	29	26	55
60 - 69	36	9	45
70 +	8	7	15
	147	100	247

Age and Sex Distribution

combination, each tablet containing 75mg of isoniazid, 75mg of prothionomide, and 50mg of dapson. Patients under the age of 16 years and adults whose body-weight was below 45 kg were given half the above-mentioned dose. More recently, it has been possible to give the required dosage of all four drugs in a fixed combination: Isoprodian–RMP. With this further development, administration is easier, thus ensuring greater patient compliance. It also avoids the possible risks of rifampicin monotherapy or blackmarketing.

Out of the 247 patients that started MDT, four patients were excluded from the programme for the following reasons. Two patients were found to be unreliable and were not taking the treatment regularly, if at all; one patient refused further treatment after 6 weeks due to persistent vertigo, while the fourth patient refused further treatment following a lepra reaction 2 weeks after starting MDT.

In conformity with the predetermined plan of the eradication programme, patients who had been found to be bacteriologically negative at the start of the programme were treated with MDT for a fixed period of 5 months. In all other cases the time of termination of therapy was determined by the clinical and bacteriological progress of the individual patient. Figure 3 shows the duration of MDT of the patients included in the programme, except for three patients who have started treatment in the last two years and are still undergoing therapy.

One hundred and four patients did not receive rifampicin throughout the whole of their treatment period, but for the first 5–10 months after which treatment was continued with Isoprodian alone for varying periods of 6–15 months. This was not done due to any adverse reaction to rifampicin, but because the clinical and bacteriological situation of these patients was sufficiently satisfactory to warrant the withholding of rifampicin from the treatment regimen with a considerable reduction in cost. (In a minor variation from the original protocol, the usual Isoprodian–rifampicin combination was replaced by the combination rifampicin (600 mg) prothionomide (300 mg) and ethambutol (1200 mg) daily for a few months in a group of 15 patients. However, since no

Lepromatous (LL+BL)	191
Borderline	5
Tuberculoid (BB+BT)	51

Figure 2. Classification of patients.

notable superior effect was recorded, the original combination was again administered.)

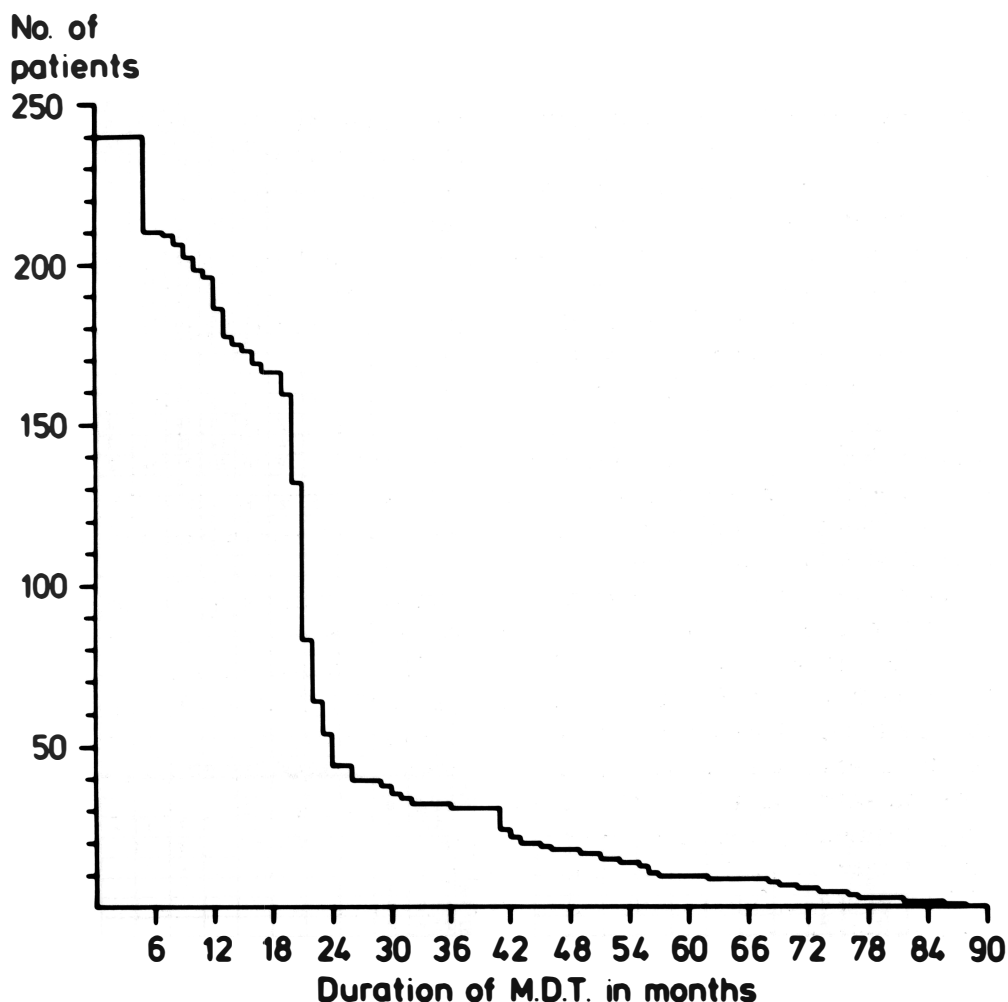
As mentioned earlier smears and biopsies were sent to Borstel regularly. Smears were flame-fixed in our clinic in Malta and sent to the reference laboratory at Borstel for staining and evaluation. The results were recorded according to the scheme shown in Figure 4. Here we see a typical course of bacteriological regression. In our opinion it is very important to get a continuous picture by taking smears monthly, and not by singular findings at long intervals. Figure 4 shows the course in a classical simple case. The analysis shows that all forms of bacteria disappear quickly, especially the 'solid' and 'fragmented' forms, while the forms listed in columns IV–VI take longer to disappear. The total regression and the concentration of these forms are very typical.

As can be seen bacteria may still be found at various times after the withdrawal of treatment. However, this is of no significance to the overall course. Finally, bacteria can no longer be detected. In the case in question, bacteria were no longer found after mid-1980. This signifies that one need not wait until the BI has reached zero to stop treatment.

The overall course of bacterial regression always follows this principle, despite all differences seen in the individual cases. The next case (Figure 5) was treated for almost three and a half years. You can see the same principle underlying the course of bacterial decline, but a longer period of time was needed until a continuous bacterial regression became evident. A relatively large number of bacteria was still to be seen for a longer period of time after withdrawal of treatment, with intermittent periods during which no bacteria were detected during the monthly check-ups. As can be clearly seen, this case could be released from treatment despite the detection of bacteria. Finally, the BI reached zero.

The recognition of the course of bacterial regression and its correlation with the clinical picture give a clear indication for the timing of release from treatment.

From a clinical point of view, the most dramatic changes in patients undergoing treatment with Isoprodian–rifampicin combination was the rapid healing of ulcerating nodules and the early regression of infiltrated lesions in lepromatous patients. Nodules and diffuse infiltration of relatively recent origin subsided in a matter of a few weeks to a few months. This was also observed in a number of patients with long-standing fibrotic lesions that were not expected to resolve to any significant degree at the start of MDT. Similar changes were recorded in patients who had signs and symptoms of mucosal involvement at the start of MDT. Nasal symptoms were relieved in the first weeks of treatment, while in three patients initially suffering from hoarseness due to laryngeal infiltration, the voice returned to normal in a few weeks. The unexpected regrowth of eyebrows in a few of the patients with madarosis was very comforting to them. This occurred mainly in those patients where the thinning or loss had first been noticed during the last two years prior to the initiation of MDT. A considerable number of patients with sensory impairment reported improvement in their



sensory ability. However, on neurological examination clinical improvement in sensation could only be recorded in a small number of cases.

Prior to the use of MDT the occurrence of Type 2 lepra reaction in patients under treatment was frequent and often severe. This is hardly surprising considering the fact that the higher proportion of leprosy patients in Malta belong to the lepromatous side of the spectrum. It had often been the practice to withhold or lower the dosage of dapsone during reactions. It was decided at the outset of the programme that no alteration in dosage should be made in the case of lepra reaction. The performance of patients with regard to lepra reaction was consequently given all due attention.

SM 00675 ¹		Date	BI	—	frag tec	granular					
LL	I					II	III	IV	V	VI	
1976	15 7	3	7	22	5	4	9	35	12	5	
	2 9	2					2	20	4	11	
	30 9	3		5	4	20	17	48	4	2	
	4 11	2				2	1	9	2	4	
30 12	2		3	2	4	2	19	5	2		
3 2	4		1	3	13	10	43	6	24		
17 3	2			4			12	2	8		
5 5	1					1	1				
14 1	1										
18 2	1						6		1		
18 3	1					1	2				
15 4	1						4	3			
13 5	3			1	3	1	64	2			
10 6	0										
8 7	0										
5 8	1						1				
2 9	2			1	3	2	5	1			
30 9	2				1	1	32				
28 10	1				1	1	1				
25 11	1						1	3			
23 12	2			2	3	3	20		2		
20 1	1						3				
17 2	0	end of treatment									
14 4	0										
12 5	0										
9 6	1					1	1	1			
7 7	1					1	1				
11 8	0										
8 9	0										
20 10	1						1				
24 11	0										
20 2	0										
22 3	1						1				
19 4	0										
17 5	0										
14 6	0										
12 7	0										
23 8	0										
11 11	0										
20 12	?										
14 2	0										
11 4	0										
6 6	0										
1 8	0										
26 9	0										
15 5	0										
10 7	0										
24 8	0										
27 11	0										
26 2	0										
21 5	0										
13 8	0										
3 12	0										
10 3	0										
2 6	0										
24 11	0										
23 3	0										
6 7	0										
5 10	0										

Figure 4. Serial bacteriological results of a typical LL case during the treatment and control periods. Bar denotes time of stopping MDT.

G J 00081		Date	BI	—	frag tec	granular					
LL	I					II	III	IV	V	VI	
1976	10 4	5	7	3	15		9	16	11	9	
	13 5	5	2	28	8	17	4	30	5	6	
	15 6	4		2	2	18	16	46	4	12	
	14 7	5		8	3	14	17	39	9	10	
16 9	2		1	8	7	19	6	6			
22 10	4		7	3	7	11	55	6	11		
1 12	3			7	12	15	47	2	17		
30 12	4		3	10	21	11	37	5	13		
26 1	3			2	9	8	56	2	23		
24 2	4		2	5	18	15	32	18	10		
24 3	4		3	3	24	6	43	12	9		
26 4	5		1	3	27	5	46	10	8		
27 5	4		2		5	2	67	2	1		
22 2	0										
9 3	2		1			1	8	2			
3 5	2		1	1	3	2	17	1	1		
14 6	2			2	3	9	18		2		
15 7	2			4	7	19	18	1	3		
6 9	3			9	18	30	71	14	2		
2 10	1						8				
22 11	3		2	8	8	7	21				
27 12	2			1	2	4	1	2			
7 3	3			7	3	75	4				
28 4	0										
26 5	3					1	50	13			
27 6	3		1	1	5	4	13	1	2		
25 7	2					1	13				
29 8	2			2			14	1	4		
10 10	2						9		2		
14 11	1						8				
19 12	1						8		1		
8 3	0										
3 5	0										
16 5	end of treatment										
16 7	1					1					
23 8	0										
8 10	2					2		17	1	4	
26 11	1							3			
11 2	1							4			
15 4	0										
10 6	0										
23 6	0										
20 10	0										
26 1	0										
22 6	0										
5 10	0										
25 7	0										
6 3	0										
7 8	0										
23 11	0										

Figure 5. Serial bacteriological results of another LL case showing a longer period of MDT.

Of the 243 patients treated with MDT, 10 had Type 1 lepra reaction, while 86 patients had one or several episodes of Type 2 lepra reaction. A considerable number of these reactions were mild, with just crops of evanescent nodules and no constitutional symptoms. Forty-two patients had one moderately severe reaction with constitutional symptoms such as: pyrexia, joint pains, myositis, etc. Two cases were severe enough to warrant hospitalization for a few days. Erythema necroticans was, however, not encountered. In 37 patients, episodes of mild reaction were also recorded during the first 2 years after stopping treatment.

Most reactions were satisfactorily controlled by the administration of 100–400 mg of thalidomide at night, dosage being varied according to severity. Corticosteroids were used in as small a number of cases as possible in view of the high incidence of diabetes in Malta.

Ocular involvement was a reasonably frequent occurrence prior to MDT, as indicated by the ophthalmic examination of the 201 patients who were admitted into the programme in June 1972. Eight of these patients had blindness of one or both eyes, while a further 23 patients had less severe involvement, such as, diminished vision, corneal opacity, sclerosing keratitis, and irregular or non-reactive pupils. During the course of our study, five patients had an episode of irido-cyclitis, all of which responded satisfactorily to treatment. It is gratifying to note that no case of blindness has ensued in the group of 46 patients diagnosed since 1972 and treated with MDT.

Out of the 116 male patients who started the programme in 1972, seven gave a past history of one or more episodes of epididymo-orchitis. However, no episode was recorded subsequent to the start of MDT in these patients or in any of the other 31 male patients who were included in the programme since 1972.

Most patients tolerated the Isoprodian–rifampicin combination without any difficulty. The commonest side-effects encountered were gastrointestinal disturbances. These included: nausea (64 cases), dyspepsia (23), vomiting (19) and anorexia (5). These side-effects were mainly reported in the first 2 or 3 weeks and abated spontaneously on further treatment in most cases. Eight patients, however, continued to suffer from occasional dyspepsia and four patients reported episodes of nausea from time to time throughout the treatment period. Other side-effects encountered in the first 4 to 6 weeks of treatment were: soreness of the mouth and tongue (28 cases), dizziness (17), and lassitude (5). An acneiform rash developed in three patients, while two patients complained of paraesthesiae. Two patients developed depressive psychosis which could have been contributed to by the treatment.

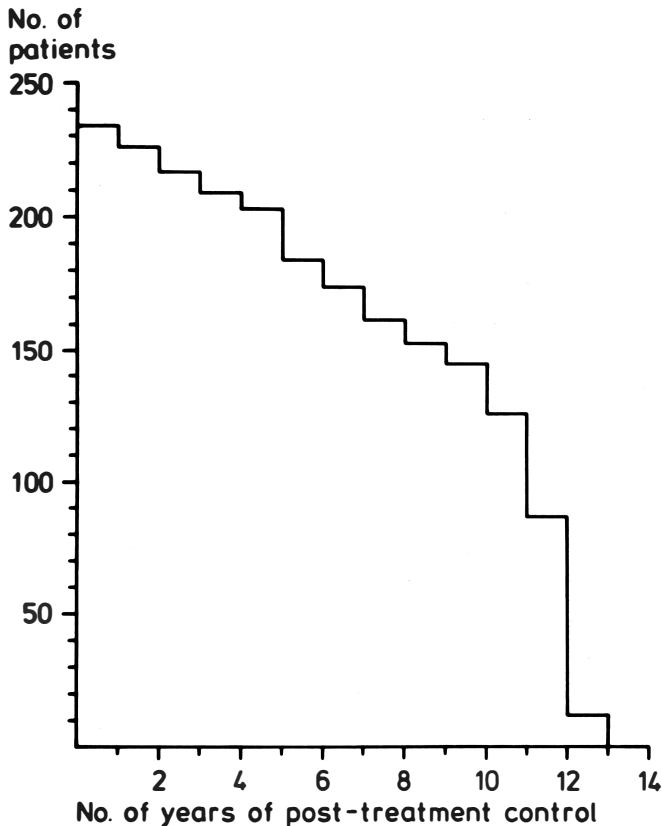
Twelve patients had moderate anaemia, while a further 21 patients had mild anaemia in the course of treatment. However, it was observed that these episodes of anaemia occurred mainly during lepra reactions. White blood counts and platelet counts were within normal limits.

Liver function tests were not routinely performed prior to 1978. Up to that time, a rise in serum bilirubin and/or serum transaminases was recorded in eight

patients. These rises were of a low grade and results returned to normal without the interruption of therapy. Two other cases developed jaundice and necessitated the suspension of antileprosy treatment until liver function tests returned to normal. When treatment was restarted the serum transaminases of one patient showed progressively increasing levels necessitating interruption of therapy, while the other patient completed her course of treatment uneventfully.

Since 1978, 18 patients have had routine fortnightly or monthly liver function tests performed during the whole of their course of treatment. Ten patients had normal LFTs throughout. Six patients showed transient elevations of serum bilirubin and/or transaminases, the levels of which returned to normal despite continuation of treatment. Two patients had progressively increasing levels of serum transaminases necessitating interruption of treatment. These settled to normal but started rising again when treatment was restarted.

There can be no doubt that in a programme like that undertaken in Malta, the aspect of post-treatment control is of the utmost importance. The incidence of relapses during this control period can be considered as a gauge of the efficacy of



the treatment regimen employed. One would expect that the majority of patients, where treatment has been ineffective, would show signs of relapse in the first 2 or 3 years following cessation of treatment. The situation in Malta from the point of view of control was ideal in that the size of the country greatly facilitated patient surveillance, thus allowing post-treatment control for a much longer period. In fact, apart from deaths due to natural causes, regular control of all 240 patients who have completed their treatment has been carried out, with the exception of only seven. Four patients have emigrated from Malta at some time during the control period, while three patients have refused to attend for further follow-up after a few years.

Figure 6 shows the duration of control for all patients who have completed their course of MDT. As can be seen from the diagram, 145 patients have been under regular control for 10 years or more, while a further 57 patients have been controlled for a minimum of 5 years. No clinical relapse was registered in any of the patients under control. In one female patient who had received MDT for a period of 5 months, a routine biopsy in the 6th year of control indicated the possibility of a bacteriological relapse. Although there was no clinical evidence of any relapse, it was considered prudent to restart treatment. The patient was given a second course of Isoprodian–rifampicin combination for 18 months and has since then been under control for over 5 years without any evidence of relapse.

I would here like to express our appreciation of the extreme cooperation we have had from the patients with regard to their regular attendance and compliance during both the treatment and control periods.

In conclusion, it may be stated that all 243 patients were treated with the same Isprodian–rifampicin combination which could be administered easily and which was well tolerated. The duration of therapy was determined by individual clinical and bacteriological progress. After treatment all patients were kept under regular control and practically no relapses were recorded.

It is of the utmost importance that the implications of the results achieved in the Malta programme are followed up by on-going observation as is presently carried out.

References

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