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SPECIAL ARTICLE

The impact of multiple drug therapy on leprosy disabilities*

MERLIN L. WILLCOX,
Keble College, Oxford OX1, UK

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Summary In an overview of controlled trials, it is shown that bactericidal drugs increase the short–term risk of Type I reactions, but prevent the long–term development of new impairments caused by bacterial proliferation. Clinical experience suggests that the clofazimine component of multiple drug therapy (MDT) has reduced the incidence of Type II reactions or erythema nodosum leprosum (ENL). The principal impact of MDT, compared with monotherapy, has been to reduce the duration of active disease, thus preventing the deterioration of disability scores. Reduction of population disability rates is mainly achieved by earlier detection and treatment. MDT has a number of indirect benefits such as improved compliance, decreased cost, and increased motivation and availability of leprosy workers. However, MDT must be supplemented by other measures to prevent and treat disabilities.

Introduction

In 1994, there were an estimated 2·4 million active cases of leprosy in the world[1] and 2–3 million people had deformities (that is, visible physical changes) caused by this disease. Unlike the closely-related disease of tuberculosis, leprosy is rarely fatal and not highly infectious. Yet the disabilities it causes can ruin lives—not only because they may prevent patients from doing their normal jobs, but also because of the social stigma attached to them.[2,3] A recent survey in India[3] found that up to 46% of deformed patients may be rejected by their families.

Disabilities are part of a continuum of the effects of leprosy, which can be divided into three tiers:[4] impairment, disability and handicap. The disease damages nerves, producing impairments in sensory and motor function. These may cause disability directly—by making certain actions more difficult—or indirectly, by allowing injuries to occur unnoticed. Affected individuals may become handicapped in society when they can no longer fulfil their normal roles.

Combinations of antibiotics were first used to treat leprosy in 1971,[5] but did not become widespread until after 1982, when the World Health Organization introduced standardized regimes: 6 months for paucibacillary patients, and 24 months for multibacillary cases.

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This article will review the impact of multiple drug therapy (MDT) on leprosy disabilities at two different levels: therapeutic (the impact on different types of impairment, which cause disabilities), and preventive (the impact on individuals with different types of leprosy at risk of becoming disabled). The search for relevant papers was conducted systematically using the MEDLINE database, and the references of these papers were also searched for other relevant publications.

The therapeutic impact of multidrug therapy on different types of impairment

Leprosy disabilities result from impairments produced by disease. The pattern of disease determines which impairments develop and what treatment is required. In lepromatous leprosy, impairments result from bacterial proliferation, whilst in tuberculoid disease, the immune response damages nerves.

To review the impact of MDT, it is most useful to consider its effect on the two main processes causing impairments: neuritis and local proliferation. Neuritis may produce permanent motor impairments (often at a site remote from the actual lesion), and sensory impairments, which allow secondary damage of tissues to occur unnoticed. Local bacterial proliferation causes specific deformities in particular anatomical sites.

NEURITIS

Neuritis is usually asymptomatic and nerve function may gradually deteriorate without the patient noticing.[6–8] This may occur in spite of chemotherapy, perhaps due to gradually increasing pressure on the nerve.[9] Paradoxically, because it goes unnoticed, silent neuritis may cause at least as many impairments as the more severe (acute) neuritis, which presents with nerve pain and/or sudden loss of function.

While antileprosy therapy is required to kill the causative organisms, it may increase the risk of neuritis,[10] for which additional treatment is needed. If treated promptly with steroids, many patients recover, or at least their nerve damage is limited.[8,10] This has prompted leprosy workers to advocate regular screening of nerve function in their patients.[6,8] The fact that nerve damage can be reversed or limited is not appreciated by all field staff; when it is, treatment and screening are much improved.[6,8]

Type I Reactions (TIRs), episodes of increased inflammatory activity in skin lesions and/or nerves,[11] are one cause of neuritis. They may result from an increase in the cell-mediated immune response and the formation of granulomata.[12] Inflammation in the nerves causes pain, but the most important consequence are motor impairments and disability. TIRs also increase the risk of arthritis.[13]

The reported incidence of TIR varies widely from study to study. The comprehensive review by Lienhardt and Fine[11] found that TIRs occur commonly during and after chemotherapy. Indeed, for patients not in TIR at the time of diagnosis, the greatest risk of TIR is in the first 6–12 months of treatment. The lack of clinical trials with long-term follow-up before the introduction of MDT makes it difficult to compare the risk of TIR under monotherapy and MDT. A retrospective study is quoted from Malaŵi which found a lower risk of TIR with MDT than with DDS monotherapy.

Table 1 summarizes the randomized controlled trials which quote incidence of TIR. In paucibacillary patients, Orege *et al.*[14] found no difference between WHO and modified regimens. Groenen *et al.*[15] found a much higher incidence of TIR in rifampicin monotherapy (B)

than in a modified MDT regimen (A) or a single dose of rifampicin (U). The allocation of patients was not entirely random—those not prepared to come to the centre weekly were automatically given MDT (A)—but this is unlikely to account for the very large difference observed.

All the other studies refer to multibacillary patients. Groenen *et al.*[15] found a significantly lower incidence of TIR with the WHO regimen than with alternative high dose rifampicin regimens. Singh *et al.*[22] also found a greater incidence of TIR and neuritis in a modified WHO regimen with high dose rifampicin, but the difference was not statistically significant due to the small numbers studied. Thomas *et al.*[21] found no difference between a regimen containing high dose rifampicin and another containing no rifampicin. Interactions with other drugs make these results hard to interpret; it seems that rifampicin may increase the risk of TIR in certain drug combinations but not in others.

Groenen *et al.*[15] found that clofazimine seemed to reduce the frequency, duration and severity of TIR as compared to dapsone. However, their groups were not randomised: patients who had taken DDS monotherapy for more than 5 years received clofazimine, and those who had not continued with DDS. The authors also found that previously untreated patients were more at risk of TIRs, so this could explain the differences between their groups. Jamet *et al.*[16] found that clofazimine monotherapy did not suppress TIRs, and that high doses could increase their incidence.

The role of dapsone is unclear. Dietrich *et al.*[17] found no difference in the incidence of TIRs between dapsone monotherapy and two MDT regimens. Barnetson *et al.*[25] found that patients receiving low dose DDS monotherapy (5 mg od) were more at risk of TIR than those receiving higher doses (50 mg od). They observe that DDS must have an anti-inflammatory effect at higher doses since 1 mg daily is the minimal dose for antibacterial activity.

Any antibacterial chemotherapy could release antigens which could stimulate the cell-mediated immune response (CMI). A histological study of patients undergoing MDT found evidence of immune activation even in patients without a TIR.[26] More potent chemotherapy such as rifampicin may carry a greater risk, but other drugs such as DDS and clofazimine may help to diminish this risk. In summary, MDT probably increases the incidence of TIR in comparison to no treatment, but may or may not do so in comparison to dapsone monotherapy.

Type II reactions (erythema nodosum leprosum (ENL)) following MDT have been studied by several researchers. ENL is thought to be an immune-complex reaction; it causes not only neuritis but also systemic effects, such as widespread subcutaneous erythematous nodules, fever and iritis.[12] It rarely results in permanent loss of nerve function, but repeated attacks occasionally cause deformities in the hands such as 'swan-neck', 'twisted fingers' or 'nonparalytic clawing'.[10] ENL may also cause acute-onset arthritis, distinct from that mentioned see p. 356. This variety usually only causes temporary disability; nevertheless, extended episodes have been reported.[27,28] Atkin's survey[28] found 22% of patients had ENL-related arthritis, of whom only one (8%) had bone erosions.

Table 2 summarizes the randomized controlled trials (RCTs) of different chemotherapy regimes for MB leprosy, together with the percentage of patients reported to have suffered at least one ENL reaction during the follow-up. Cellona *et al.*[29] quoted a percentage for each year rather than an overall figure; the maximum for each year is reported in the table. Unfortunately percentages are not comparable between studies because of the varying follow-up periods, and because there is no indication of the severity of reactions. However, comparisons between groups within any study should be valid.

Starting any chemotherapy increases the risk of ENL, compared to no treatment.

Table 1. Randomised–Controlled Trials of MDT for PB and MB leprosy and incidence of Type I reactions

Ref	T	N		Treatment regimen	TIR (% of patients)	Acute Neuritis (%)
14 PB	1½ yr	64	A:	WHO–PB–MDT	23·3	
			B:	RMP 1500 mg 1/3 m, DDS 100 mg od, 6 m	20·3	
15 PB	>1 yr	184	A:	RMP 1500 mg 1 x DDS 100 mg od, 1 yr	2·2	
		59	B:	RMP 900 mg 1/wk, 10 wk	18·6	
		92	U:	RMP 40 mg/kg 1x	5·4	
15 MB		129	C:	RMP 600 mg od, 6 m ETH 500 mg od, 6 m either DDS or CLO, 100 mg od, 1 yr.	55	
		128	D:	RMP 600mg od, 6m ETH 500mg od, 1y either DDS or CLO, 100mg od, 1y.	45	
		23	W:	WHO–MB–MDT	17	
16 MB	6 m	16	A:	CLO 50 mg od, CLO 300 mg 1/m, 6 m	13	
		13	B:	CLO 600 mg 1/m, 6 m	8	
		16	C:	CLO 1200 mg 1/m, 6 m	44	
17 MB	8–11 yr	64	A:	DDS 100 mg od, ≥3 yr	(over the entire follow–up)	
		83	B:	DDS 100 mg od	18 (LL)	
				RMP 600 mg od, ≥3 yr	38 (BL)	
		81	C:	DDS 50 mg bd RMP 600 mg od PTH 175 mg bd INH 175 mg bd, ≥3 yr	No differences according to treatment	
18 MB	2 m	8	A:	OFL 400 mg od, 2 m	0	
		8	B:	OFL 800 mg od, 2 m	0	
		8	C:	OFL 400 mg od DDS 100 mg od CLO 300 mg 1/m CLO 50 mg od, 2 m	0	
19 MB	6 m	4	A:	MIN 200 mg od, 1 m, then 100 mg od, 6 m	0	
		8	B:	MIN 100 mg od, 6 m	0	
		2	C:	MIN 100 mg 6/m, 1 m, then 100 mg od, 5 m	0	
20 MB	2 m	11	A:	MIN 100 mg od, 2 m	0	
		12	B:	CLT 500 mg od, 2 m	0	
		12	C:	MIN 100 mg od, CLT 500 mg od, 2 m	0	
21 MB	5yr	88	A:	RMP 600 mg od, 3 m INH 300 mg od, 3 m DDS 100 mg od, 5 yr CLO 100 mg od, 5 yr	9·1	14·8
		89	B:	DDS 100 mg od, 5 yr CLO 100 mg od, 5 yr	7·9	10·1
22 MB	6m	15	L1:	WHO–MB–MDT, 6m	13	0
		15	L2:	RMP 600 mg od, 21d, DDS 100 mg od, 21d, CLO 100 mg od, 21d, then WHO–MB–MDT, to 6 m	20	7

Table 1. *(Continued)*

Ref	T	N	Treatment regimen	TIR (% of patients)	Acute Neuritis (%)
23	3 yr	157	M18: WHO–MB–MDT, 18 m	38·9	
MB	(mean)	148	M30: WHO–MB–MDT, 30 m	32·4	
24	2+	31	V: RMP 600 mg od, 2 wk,	27	26
MB	yr		DDS 100 mg od, 2 wk,	(12 LL,	
			CLO 50 mg od, 2 wk,	36 BL,	
			then WHO–MB–MDT, 2 yr	36 BB)	
			Vaccine:		
			1×10^9 bacilli, 1 x,		
			then 5×10^8 bacilli, 1/3 m, 2 yr		
		25	C: Drugs as above,	14	22
			Placebo 'vaccine',	(0 LL,	
			1/3 m, 2 yr	40 BL,	
				9 BB)	

Abbreviations:

T, length of follow–up period; N, number of subjects.

CLO, clofazimine; CLT, clarithromycin; DDS, dapsone; ETH, ethionamide; INH, isoniazid; MIN, minocycline; OFL, ofloxacin; PTH, prothionamide; RMP, rifampicin; THI, thiacetazone.

WHO–PB–MDT, WHO regimen for PB leprosy (RMP 600 mg 1/m, DDS 100 mg od, 6 m).

WHO–MB–MDT, WHO regimen for MB leprosy (RMP 600 mg 1/m, CLO 300 mg 1/m, CLO 50 mg od, DDS 100 mg od, 2 yr).

od, once daily; bd, twice daily; 1 x, single dose; 1/m, once a month; 1/3m, once every three months.

d, day(s); wk, week(s); m, month(s); yr, year(s).

Becx-Bleumink[32] reports a substantial rise in the number of ENL reactions during the first year of MDT, as compared to the time of diagnosis. Bwire & Kawuma,[33] in a 5-year study of 2317 leprosy patients in Uganda, found that 17 of 18 patients with ENL were on MDT. However, the incidence of ENL has decreased since MDT replaced monotherapy. ENL used to occur in 50% of LL patients and 30% of BL patients.[34] Since the introduction of MDT, ENL has become less common,[35,36] occurring in only about 20% and 10% of LL and BL patients respectively (Lockwood D.N.J., personal communication).

It is a pity that the only trial comparing monotherapy with MDT[17] did not use WHO MDT; the MDT regimen used contained larger doses of rifampicin and did not include clofazimine. Not surprisingly, there was no significant difference in the incidence of ENL between groups. Large doses of rifampicin may increase the risk of ENL, while clofazimine may decrease it.

Clofazimine is known to be anti-inflammatory as well as bactericidal.[6,37,37a] Treatment of ENL by clofazimine has been reported by Burte *et al.*[37] All the symptoms of neuritis, with the notable exception of anaesthesia, showed complete recovery in 15 of their 20 patients treated for ENL with clofazimine, and the severity of the reaction was reduced in the five others. Helmy *et al.*[37a] found that clofazimine was significantly better than placebo for the treatment of ENL in a small double-blind randomized crossover trial.

Clofazimine is believed to be responsible for the decreased risk of ENL observed since the introduction of WHO–MDT (Lockwood D.N.J., personal communication). Unfortunately, no trials of sufficient quality have been conducted to prove this. Cellona *et al.*[29] found that clofazimine suppresses ENL: patients on their regimens IIA, IIB and IIC, which included

Table 2. Randomized–controlled Trials of MDT for MB leprosy and incidence of ENL reactions [for key to abbreviations, see Table 1]

Ref	T	N	Treatment regimen	ENL (% of patients)
15		129	C: RMP 600 mg od, 6 m ETH 500 mg od, 6 m either DDS or CLO, 100 mg od, 1 yr.	11
		128	D: RMP 600 mg od, 6 m ETH 500 mg od, 1y either DDS or CLO, 100 mg od, 1 yr.	16
		23	W: WHO–MB–MDT	0
17	8–11 yr	64	A: DDS 100 mg od, ≥3 yr	(over the entire follow–up)
		83	B: DDS 100 mg od RMP 600 mg od, ≥3 yr	49 (LL) 35 (BL)
		81	C: DDS 50 mg bd RMP 600 mg od PTH 175 mg bd INH 175 mg bd, ≥3 yr	No differences according to treatment
29	5 yr	97	IA: DDS 100 mg od, 5 yr RMP 1200 mg 1x	(maximum in any year) 45
		32	IB: DDS 100 mg od, 5 yr RMP 600 mg od, 4 wk	45
		39	IC: DDS 100 mg od, 5 yr RMP 1200 mg, 1x CLO 100 mg 3/wk, 24 wk	42
		34	ID: DDS 100 mg od, 5 yr RMP 1200 mg, 1x PTH 375 mg od, 8 wk	45
		83	IIA: CLO 100 mg 3/wk, 5 yr RMP 600 mg od, 4 wk	22
		16	IIB: CLO 100 mg 3/wk, 5 yr RMP 600 mg od, 2 wk	21
		28	IIC: CLO 100 mg 3/wk, 5 yr RMP 1200 mg 1/m, 6 m	32
		29	IID: RMP 600 mg od, 4 wk, then 600 mg 2/m, 5 yr PTH 375 mg od, 8wk, then THI 150 mg od, 5 yr	37
18	2 m	8	A: OFL 400 mg od, 2 m	0
		8	B: OFL 800 mg od, 2 m	0
		8	C: OFL 400 mg od DDS 100 mg od CLO 300 mg 1/m CLO 50 mg od, 2 m	25
19	6 m	4	A: MIN 200 mg od, 1 m, then 100 mg od, 6 m	0
		8	B: MIN 100 mg od, 6 m	0
		2	C: MIN 100 mg 6/m, 1 m, then 100 mg od, 5 m	0
20	2 m	11	A: MIN 100 mg od, 2 m	9
		12	B: CLT 500 mg od, 2 m	8
		12	C: MIN 100 mg od, CLT 500 mg od, 2 m	25
21	5y	88	A: RMP 600 mg od, 3 m INH 300 mg od, 3 m DDS 100 mg od, 5 yr CLO 100 mg od, 5 yr	31·8

Table 2. *(Continued)*

Ref	T	N	Treatment regimen	ENL (% of patients)
		89	B: DDS 100 mg od, 5 yr CLO 100mg od, 5yrs	38·2
30	2 y	47	I: RMP 600 mg od, 9 m, then 600 mg 1/m, 9 m DDS 100 mg od, 2 y CLO 50 mg od, 2 y	25·5
		41	II: WHO–MB–MDT, 2 y	7·3
22	6 m	15	L1: WHO–MB–MDT, 6 m	0
			L2: RMP 600 mg od, 21 d, DDS 100 mg od, 21 d, CLO 100 mg od, 21 d, then WHO–MB–MDT, to 6 m	0
23	3 yr (mean)	157 148	M18: WHO–MB–MDT, 18 m M30: WHO–MB–MDT, 30 m	3·2 2·7 (NB: severe ENL only)
24	≥2 yr	31	V: RMP 600 mg od, 2 wk, DDS 100 mg od, 2 wk, CLO 50 mg od, 2 wk, then WHO–MB–MDT, 2 yr Vaccine: 1×10^9 bacilli, 1x, then 5×10^8 bacilli, 1/3m, 2 yr	29 (35·2 LL, 21·4 BL)
		25	C: Drugs as above, Placebo 'vaccine', 1/3m, 2 yr	28 (40 LL, 10 BL)
31	≥2 yr	37	V: as above	27 (35 LL, 14 BL)
		34	C: as above	35 (50 LL, 14 BL)

regular clofazimine for 5 years, had a much lower incidence of ENL than those on other regimens. However, this trial was not truly randomized: subjects in group I were all newly-diagnosed patients whereas those in group II were all relapsed patients previously treated with dapsone monotherapy. Groenen *et al.*[15] found no difference in incidence of ENL, whether clofazimine or DDS was used as the third drug; but as discussed above, this trial was not randomized either. Furthermore, the effect of clofazimine could have been masked by large daily doses of rifampicin and/or ethionamide. Regimens containing these had a higher incidence of ENL than the WHO regimen, although a much smaller number of patients took the WHO regimen. Ji *et al.*[18] found more ENL in the regimen containing clofazimine and dapsone than in the regimens containing ofloxacin alone, but the number of subjects in their trial was too small for chance differences to be ruled out.

Rifampicin, known to be potently bactericidal, could increase the risk of ENL because of the rapid breakdown of bacilli and release of antigens into the circulation, which could then form the immune complexes believed to be involved in ENL.[12] This hypothesis is supported by Jadhav *et al.*,[30] but not by Thomas *et al.*[21] or Singh *et al.*[22] The trial by Jadhav *et al.*[30] seems to be the best test of high dose rifampicin: it found a much higher rate of ENL in the

regimen containing daily rifampicin for 9 months than in the standard WHO regimen. Thomas *et al.* gave rifampicin for three months only; Singh *et al.* gave it for 21 days, before reverting to WHO–MDT.

Motor and sensory impairments themselves have not been widely studied in relation to the impact of MDT. However, several researchers have investigated lagophthalmos. This motor impairment prevents normal eye closing and predisposes to corneal damage and loss of visual acuity, and may account for a large proportion of leprosy-related potentially blinding disease (35% in one study[38]).

Lagophthalmos occurred in 3·7% of the 678 patients surveyed by Waddell & Saunderson;[39] no link was found with type of treatment (monotherapy or MDT). In some cases, the lagophthalmos improved during chemotherapy. In a survey of 640 MB patients, Courtright *et al.*[38] found lagophthalmos in 3.8% of newly-diagnosed cases and in 10.2% of patients previously on DDS monotherapy. Good compliance with MDT diminished the risk (to 3%) and poor compliance increased the risk (to 50%). However, others[40] claim that the risk of lagophthalmos is raised in the first 6 months of MDT (presumably due to TIRs).

Plantar ulcers, the result of sensory impairment, were studied by Mane *et al.*[41] Ulcers were prevented by MDT, but not in patients who already had a sensory impairment at the start of therapy. For these, disability is best prevented by basic preventive measures such as protective shoes which are attractive enough for patients to wear.[6,42] MDT usually limits the further development of anaesthesia; but it does not always restore sensation which has already been lost.

SPECIFIC DEFORMITIES

Specific deformities occur in patients with lepromatous (LL and BL) leprosy. Some specific impairments are caused simply by local proliferation of bacteria, while others are caused by Type 2 or ENL reactions.

Iritis is an example of a localised infection which may result in a specific impairment, and eventually blindness. The best data on MDT and iritis comes from a prolonged follow-up study of 678 patients in Kasese District, Uganda.[39] Twelve per cent of patients surveyed had iritis, of whom 33% had visual loss in one or both eyes. Iritis was the primary leprosy-related cause of visual loss. The risk of iritis was not significantly greater in patients who received rifampicin late or not at all, compared to those who received it within a year after diagnosis (adjusted odds ratio = 1·8, 95% confidence intervals 0·88–3·9). MDT was not always immediately successful—four patients still suffered from iritis after 2–11 years of rifampicin. Iritis need not cause damage if treated early; the improved prognosis in recent years may result from improved overall management and earlier presentation, rather than MDT alone.

Nasal deformities are prevented by prompt chemotherapy, according to Srinivasan.[10] Within a few months of starting treatment, bacilli are cleared, mucosal ulcers heal and granulomas resolve. Some disfigurement may persist and require plastic surgery. Unfortunately, there is little published work comparing the effect of MDT with that of monotherapy on the incidence of nasal damage. Since it is caused by bacterial proliferation, any antileprosy chemotherapy would be expected to help.

Arthritis may be caused by localized proliferation of bacteria in the joints, or an immune mediated reaction against synovium. In a survey of 66 patients in an Egyptian leprosy colony, Atkin *et al.*[28] found 20 (30%) had an inflammatory symmetrical peripheral polyarthritis. 11 of these patients (55%) showed presence of bone erosion on radiography. All of the patients had

pain on active and passive movements of the joints, which may have been disabling. Treatment with MDT led to slow resolution of the arthritis and associated morning stiffness and joint pains. In some patients, the onset of arthritis coincided with noncompliance. Unfortunately the arthritis never resolved completely, although acute exacerbations became less frequent and less severe on MDT. Some patients had permanent structural deformities. However Singh and Kaur, in a study of 60 patients in India, found no evidence of bone erosion, and joint symptoms resolved completely in most patients after one year of MDT.[13]

In summary, MDT largely prevents the development of new impairments caused by bacterial proliferation. Rifampicin is very effective at killing bacteria. But it may precipitate damaging immune reactions, probably due to the release of bacterial antigens. Clofazimine, through its anti-inflammatory effect, may help to prevent Type II reactions.

The preventive impact of multidrug therapy on leprosy disabilities

Apart from neuritis, the most important drug-related risk factor for the development of impairments and disabilities is the duration of active disease. The impact of MDT on this will be reviewed, firstly for paucibacillary, then for multibacillary patients. Then it will be considered whether MDT can improve the 'disability scores' of patients.

PAUCIBACILLARY PATIENTS

In paucibacillary leprosy, dapsone monotherapy was prescribed for 3–5 years and the average time to reach inactivity was $15 \pm 8{\cdot}6$ months.[44] Table 3 shows the percentage of patients whose lesions become inactive after 6, 12 and 24 months, under different PB drug regimens. While definitions of inactivity vary from study to study, large differences between studies probably indicate true differences, and comparisons within studies are valid.

Husser *et al.*,[43] comparing DDS monotherapy with two short regimens of rifampicin monotherapy, showed clearly that it takes two years before most cases become inactive. At one year, fewer DDS cases have reached inactivity than rifampicin cases. In comparison, Bhate *et al.*[44] found that the majority of cases treated with two different MDT regimens became inactive within one year (average time to reach inactivity is $6{\cdot}95 \pm 2{\cdot}13$ months for I and $8{\cdot}21 \pm 2{\cdot}84$ months in group II). Orege *et al.*[14] also found that most patients on the WHO regimen reached inactivity by 8 months. The modified MDT regimen—two large doses of rifampicin at an interval of three months—produced inactivity within six months. Becx-Bleumink[32] found that after 6 months on WHO–MDT, 114 (30·3%) of 963 patients still had active skin lesions. Treatment was stopped according to the protocol and the skin lesions became inactive within two years in all except one of the 114 patients. The single-dose MDT regimens studied by Pattyn *et al.*,[45,46] potentially convenient and inexpensive, show a much slower progression to inactivity. The MDT regimen recommended by WHO dramatically reduced the duration of active disease in most paucibacillary patients; some other regimens may have an even greater impact. Thus MDT has prevented the development of impairments and disability in many PB patients.

MULTIBACILLARY PATIENTS

Curtailing the duration of active disease is especially important in MB leprosy, as nerve

Table 3. Randomized-controlled trials of MDT for PB leprosy; % of patients with all lesions inactive at 6 months, 1 year and 2 years

Ref	N	Treatment regimen	6 m	1 yr	2 yr
43	24	A: DDS 100 mg od, 3 yr	N/A	0–33	66–91*
	29	B: RMP 900 mg 1/w, 8 wk	N/A	28–57	51–86*
	22	C: RMP 900 mg 1/w, 12 wk	N/A	37–62	77–95*
44	40	A: RMP 600 mg 1/m, 6 m DDS 100 mg od, 1½ yr	50·0	92·5	N/A
	40	B: RMP 600 mg 1/m, 6 m CLO 100 mg 1/2d, 6 m DDS 100 mg od, 1½ yr	40·0	85·0	N/A
14	64	A: WHO–PB–MDT	63·3	83·0	N/A
	63	B: RMP 1500 mg 1/3 m, DDS 100 mg od, 6 m	82·3	88·1 (at 8 m)	N/A
45	247	A: RMP 1500 mg, 1x, DDS 100 mg od, 1 yr	N/A	12–22	56–67†
	240	U: RMP 40 mg/kg, 1x	N/A	8–24	53–54†
46	223	C2: RMP 40 mg/kg, 1x CLO 1200 mg, 1x	N/A	N/A	66·8–73·5‡
	212	C4: RMP 40 mg/kg, 1x CLO 100 mg, 1x DDS 100 mg, 1x ETH 500 mg, 1x	N/A	N/A	71·6–77·6‡

Abbreviations: see Table 1. 1/2d, once every two days.

N/A, not available, i.e. not quoted in the paper.

* Range from worst hypothesis (regressive lesions counted as uncured) to best hypothesis (regressive lesions counted as cured).

† Range across different patient groups, according to number of skin lesions and bacteriological index (0 or 1).

‡ 95% confidence intervals.

damage and paralysis occur only late in the course of the disease,[12] and the risk is much greater than in PB leprosy.[39] Yet duration of active disease is much more difficult to assess in MB than in PB patients.

The mouse footpad test involves inoculating mice with 10^4 *Mycobacterium leprae* from the patient, and checking for replication. If the test is negative, it simply implies that there are fewer than one viable organism per 10^4 inoculated.[47] There may still be some undetected 'persisters' in the patient, which could cause a relapse. Nevertheless, this test is useful in the initial stages of therapy to determine the speed of killing. An untreated MB patient may harbour 10^{11} *M. leprae*, of which 10^{10} may be viable. This technique has shown that *M. leprae* from the lesions of MB patients no longer infect mice after different periods according to the drug regimen (Table 4). Single-dose rifampicin (600–1500 mg) is clearly the best bactericidal treatment; there is no evidence in these studies to suggest that other drugs potentiate its effect in killing *M. leprae*.

Clinical evaluation of the duration of active disease is also important. The single randomized-controlled trial comparing DDS monotherapy with MDT[17] found that 20% of patients treated by monotherapy (group A) still had clinically 'progressive' disease at 6 months, compared to 0% of those on MDT (Figure 1). The three groups were broadly comparable, but more of group A had nerve motor function impairment (26% compared to

Table 4. Period after which *M. leprae* from MB patients are no longer infective to normal mice[47,48]

Regimen	Period	Ref
DDS 50–100 mg od	100d	47
CLO 100–200 mg od, or 100 mg 3/wk	150d	16, 47
RMP 600–1500 mg 1x	7d	47, 48
CLT, 500 mg od	28 d	20
MIN, 100–200 mg od	56d	19, 20
OFL 400–800 mg od	28d	18, 49
PEF 800 mg od	56 d	49

Abbreviations: see Table 1.

18% in B and 16% in C) and thickening of nerves (31%, compared to 21% in B and 19% in C). These may indicate an advantage of MDT, or more active disease at the outset of treatment in those given the DDS monotherapy. However, given the above data for the bactericidal impact of rifampicin, the first explanation is the most likely.

DISABILITY SCORES

The ideal test of the impact of MDT on disabilities in different individuals would be to monitor their 'disability scores' before and after treatment. Unfortunately the few studies that have done this do not use a common scoring system. WHO scales do not differentiate between deformity and disability, and significant changes can occur in the extent of disability without a change in the disability grades.[11]

Smith[50] notes that those with impairment naturally tend to deteriorate. Chemotherapy may help to prevent this deterioration. Smith & Parkhe[51] failed to find a change in the mean disability index of 153 patients after four years of DDS monotherapy. Pönnighaus & Boerrigter[23] found that MB patients receiving only 18 doses of WHO–MDT had a higher risk of developing disabilities than those receiving 30 doses. Groenen *et al.*,[15] in a prospective study of 335 PB and 280 MB patients taking various regimens (MDT, RMP monotherapy) found that deformity scores remained unchanged in 95% of patients, deteriorated in 3% and improved in 2%. Richardus *et al.*[52] obtained similar results: 1·6% of previously normal patients developed nerve function impairment and 1·3% with impairment recovered by the end of treatment; corresponding figures for MB patients were 7·9% and 4·0% respectively.

DISABILITY RATES

It is notoriously difficult to measure the level of disabilities in different populations if one adheres to the strict definition of disability as 'any restriction or lack of ability to perform an activity in the manner as within the range considered normal for a human being'.[50] It has been argued that any impairments should be taken into account because 'Grade I disabilities' may deteriorate into 'Grade II disabilities' unless preventive action is taken.[53] Nevertheless most studies take account only of 'Grade II' disabilities.

The prevalence, or proportion of *all* leprosy patients with disabilities (grade II) at a single point in time, is given by several surveys. It varies from 60% in Nigeria in 1988[54] to 12% in

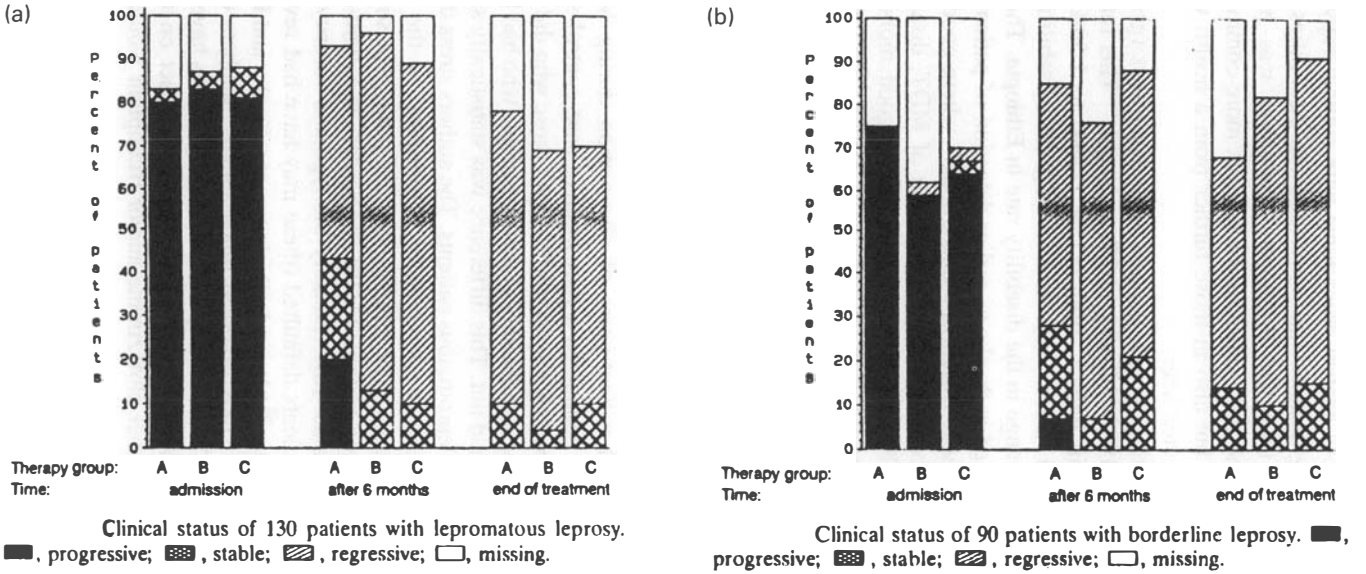

Figure 1. Clinical status of patients with MB leprosy: Group A: (N = 68) DDS 100 mg od; Group B: (N = 77) DDS 100 mg od, RMP 10 mg/kg od; and Group C: (N = 75) DDS 100 mg od, INH 350 mg od, PTH 350 mg od, RMP 10 mg/kg od. (Reproduced with permission from Dietrich *et al.*[17])

India in 1989.[53] Smith & Parkhe[51] demonstrated a decline in the proportion of patients with disabilities in spite of an increase in the number of cases of leprosy from 1979 to 1983 in India. They claimed that the leprosy control programme with monotherapy had slowed the deterioration in those with existing disability and prevented new disabilities. However, early detection of new cases before they had developed disabilities was probably equally important. Courtright *et al.*[55] found that ocular morbidity was more common in those who did not comply with their MDT, but also in those further from a health worker or health centre, who would have been detected later.

The disability rate, or proportion of *new* patients with disabilities (grade II) has been measured as 10·9% in China in 1982–3[56] and 12·7% in Nepal.[57] This rate has decreased following introduction of MDT in India,[58] from 6·15% (1984) to 1·50% (1987), and in Ethiopia,[32] from 20·6% (1984) to 13·9% (1989). However if grade I disabilities are also taken into account, there has been no change in the disability rate in Ethiopia. That the proportion with severe disabilities has declined is thanks to earlier detection of patients rather than an effect of MDT *per se*.[32] In Thailand,[59] Malawi[60] and China,[61] where good leprosy control programmes were already in place before the introduction of MDT, disability rates have remained stable. Yet in French Polynesia, which also had a good monotherapy control programme, the disability rate was stable at an average of 31·5% until the introduction of MDT when it dropped to an average of 11·7%.[62] This may have been thanks to household contact training, leading to better detection in children below the age of 15. The risk of disability is lower for younger patients.[63] Conversely, disability rates have increased in Bhutan despite the introduction of MDT, because fewer mass surveys are being done to detect patients early; these have become uneconomical as the prevalence of leprosy has fallen.[64]

The incidence of impairment during treatment is fairly low: 11·1% of patients receiving DDS for 5 years in India;[65] 2% of patients after 2–7 years of DDS chemotherapy in Trinidad and Tobago;[66] and 0·7 per 1000 patient-years of observation during MDT in India.[67] However, Radhakrishna & Nair[65] conducted a retrospective case-control study of patients on DDS monotherapy who developed leprosy disabilities and those who did not. They found that the incidence of disabilities was significantly higher in patients who had been taking their drugs regularly than in those who had not. This difference was statistically significant for PB and borderline patients, but not for lepromatous patients. The authors stress that they assessed regularity of drug-taking *before* the development of deformities; so the result is not an artefact due to deformed patients being more motivated to take drugs. The study suggests that regular DDS increases the risk of impairments for PB and borderline patients, possibly due to the increased risk of Type I reactions. Unfortunately the type and severity of impairments were not recorded, and 30% of patients defaulted (these may have had severe disabilities). This finding was replicated by Gupte,[68] also in India, but not by Keeler and Ryan in Trinidad and Tobago.[66] However the latter study involved much smaller numbers of patients (529, compared to 5746 in study 65 and 2608 in study 68). No similar studies have been conducted for MDT, so it is not clear whether it would have the same impact on the incidence of disabilities as DDS alone, or whether clofazimine and/or rifampicin would protect against development of deformities.

MDT itself cannot affect the disability rate, which declines in response to earlier case detection. The incidence of impairments during treatment may be lower with MDT than with monotherapy, but this has yet to be proven definitively. It would be especially interesting to know whether those who take their MDT regularly are more or less likely to develop deformities than those who take it less regularly.

Discussion

MDT has a number of advantages over DDS monotherapy, which it has superceded. As well as its preventive and epidemiological impacts described above, MDT may have a number of important indirect effects. Compliance is improved,[69,70] partly because the regimens are shorter. Cost is also reduced.[69] Self-reporting may increase when patients know there is an effective treatment;[71] this has been observed in Bhutan,[64] although not in Malawi[60] or in all areas of China.[61] The caseload of leprosy workers decreases dramatically as patients are released from control much faster;[72–75] this releases time for surveillance work, prevention and treatment of disabilities.[53] The more frequent (monthly) contact between health workers and patients, for supervised administration of rifampicin, provides more opportunities for health education and disability prevention.[74] The greater efficacy of MDT may have motivated health workers to improve drug coverage and routine assistance to patients with leprosy,[76] stimulating better compliance, and setting in motion a virtuous circle.

Yet MDT also has its disadvantages. It does not eliminate microbial antigens from nerves, which may perpetuate neuritis and cause further impairments long after the patient is 'cured'.[77] For example, corneal sensation sometimes continues to decrease long after the completion of MDT,[78] and this leads to loss of vision. Second, allocation of patients to the PBor MB regimen is not always easy.[32,76] The higher cost of MDT in the short term[79] may be prohibitive in impoverished areas where leprosy is commonest. It would be tragic if statistics of declining global prevalence were misinterpreted to justify reduced funding for the treatment of leprosy.[80]

The problem of leprosy disabilities cannot be solved by MDT alone. Other approaches are also necessary, both to prevent disabilities and to help those already afflicted. These have often been neglected while the WHO has vigorously promoted MDT. Most important for prevention are early case-finding and adequate treatment of reactions, and also improvements in infrastructure and socioeconomic conditions. Good housing and schooling both decrease the risk of leprosy.[81]

Those who are already disabled need re-ablement, disability prevention and rehabilitation.[4] Programmes to prevent and treat disabilities have the added bonus of improving compliance with MDT.[74] Although MDT improves the recovery of lost function (50%, compared to 20% with monotherapy in Malawi[82]), it cannot cure many deformities. 8·3% of leprosy disabilities could be reversed by surgery, health education and physiotherapy.[63] Health education is important to prevent new disabilities from developing when the patient has lost sensation and/or movement in a part of their body. New habits for living and working must be learnt and harmful old habits discarded. This involves behaving differently from others, possibly provoking ridicule, so the support of family and neighbours must be enlisted.[4] Last but not least, rehabilitation is necessary to re-integrate disabled patients into society and to help them lead as normal a life as possible. Although some aid agencies are doing rehabilitation work it is relatively expensive: it costs £44 to establish a vegetable business, and £141 to train a tailor.[83] Therefore it has been argued that the money would be better spent on improving MDT coverage to prevent new disabilities from occurring.[84]

Conclusion

MDT has had an impact on leprosy disabilities, especially by stopping active disease and so

preventing the development of disabilities in the long term. This benefit outweighs the short-term cost of increased risk of immune reactions which may result in impairment and disability. Not surprisingly, MDT has had no impact on already existent disabilities, nor on the incidence of disabilities in untreated patients. These last two problems must be tackled by other means. Although the number of registered cases of leprosy has declined dramatically, many 'cured' people still suffer from disabilities and need re-ablement, health education and rehabilitation. These must be promoted in conjunction with MDT to tackle effectively the age-old problem of leprosy disabilities.

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