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Relapses after multidrug therapy for leprosy: a preliminary report of 22 cases in West Nepal

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Summary. The WHO recommended multidrug therapy regimens for leprosy patients were implemented in Nepal from 1982. Therefore a considerable number of both paucibacillary (PB) and multibacillary (MB) patients have been on observation after release from MDT, for as long as 4–5 years. A retrospective study was done considering the patients who relapsed during this period and who were registered at the Out-patients Department of Green Pastures Hospital in Pokhara, Nepal. A total of 22 patients relapsed out of 927 who were released from MDT.

Introduction

Very little has been published on relapse after MDT, because the WHO–MDT regimens have only recently been implemented in most leprosy control projects. The WHO recommendations for the multidrug treatment of leprosy were published in 1982[1]— paucibacillary patients (PB): I, TT, BT leprosy in the Ridley & Jopling classification, with Bacteriological Index (BI) less than 2 at any one site, were to be treated with a 6-month course of DDS and rifampicin; and multibacillary patients (MB): classified as BB, BL and LL, with a BI of $\geqslant 2$ at any one site, are to be treated with the combination of DDS, clofazimine and rifampicin for a minimum of 24 months. These recommendations were implemented in Nepal from 1982. The only differences being that:

1 Because of the huge logistical problems in Nepal, patients who live too far away from the health post to come monthly, but who can attend bi-monthly, are given 1 monthly doses of rifampicin, or rifampicin and clofazimine to take unsupervised at home, in between their clinic visits.
2 All smear positive patients have been treated with MB–MDT.

Patients, materials and methods

Green Pastures Hospital in Pokhara is a referral centre for leprosy patients in the west of Nepal and has 1465 out-patients on register. Of these, 927 patients are on observation after release from MDT (555 PB and 372 MB). Of the 538 patients still on treatment, 334 are on MDT and 204 are on monotherapy (MT).

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TREATMENT REGIMENS (according to WHO)

PB patients: DDS 100 mg once daily and rifampicin 600 mg monthly for 6 months. After this, a patient is released from treatment (RFT) and put on observation (yearly) for another 4 years.
2 MB patients: DDS 100 mg and clofazimine 50 mg daily, and rifampicin 600 mg and clofazimine 300 mg monthly for a minimum of 24 months.

CRITERIA FOR RELEASE FROM MB–MDT

Clinically inactive and at least 2 sets of negative skin-smears (routine sites: (R) earlobe, (R) elbow, (R) knee and a nasal smear. Additional smears from lesions where indicated), 4 or more months apart. After release a patient is put on observation for 8 years.[2]

Since the introduction of MDT in our hospital, 40 patients were registered as having relapsed after release from either PB or MB MDT. After careful examination of the clinical records, 18 patients were excluded from this study, either because of initial misclassification, or failing to meet the criteria for release from MDT (see above) or the criteria for relapse (see below).

RELAPSE IS DEFINED AS

'A return of active disease in a patient who has apparently completed a prescribed course of treatment and whose treatment was therefore stopped by an authorized member of the health services.'

'Active disease' in leprosy can either indicate bacteriological activity, due to viable, multiplying *Mycobacterium leprae* or immunological activity due to the presence of (residual) *M. leprae*-antigen in the tissues; the latter is of course not a true relapse.

FEATURES OF RELAPSE/ACTIVE DISEASE

Time:	Slow in onset
Clinical features:	New signs of activity appear:
	a New lesions
	b Extension of existing lesions
	c Erythema
	d Neuritis
	e New nerve function loss (without clinical signs of neuritis)
	f Eye symptoms, e.g. iritis
Bacteriology:	A previously negative BI becomes positive $\geqslant 2+$.
	A single $1+$ finding is not sufficient.
Histology:	Signs of active leprosy in a skin/nerve biopsy.

We realize that quite a few of the symptoms and signs of 'active disease' also could fit the diagnosis 'reversal reaction'. The decision is usually based on clinical judgement. It is very much a diagnosis made under field conditions.

Results

Table 1. Number of relapses according to sex

Type	No. of relapses	M	F
BT	16	10	6
BL	4	4	—
LL	2	2	—

Table 2. Time of relapse (relapse interval)

	No. of patients			
	1 yr	1–2 yr	2–3 yr	3–4 yr
BT	3	2	9	2
BL	—	3	1	—
LL	—	1	1	—
Total	3 (14%)	6 (27%)	11 (50%)	2 (9%)

Table 3. Signs of relapse

Class	Positive BI	Lesions*	Neuritis	NFL	Reaction	Iritis	Paresthesia
BT	2	10	3	3	1	—	4
BL	2	—	1	1	—	1	—
LL	1	1	—	—	—	—	—
Total	5 (23%)	11 (50%)	4 (18%)	4 (18%)	1 (4·5%)	1 (4·5%)	4 (18%)

* No histoid nodules were found in any of these patients, but usually hypopigmented, hypaesthetic, or anaesthetic macules.

NFL, nerve function loss.

PAUCIBACILLARY GROUP

In the paucibacillary group 16 relapses were found. All of these patients were clinically classified as BT and all had 3 or more areas of the body* involved at the initial examination. 'Involved' means: signs of skin or nerve lesions present, therefore, e.g. dryness, ulcers, clawing and absorption are also counted as 'involvement'. All but one patient received PB–MDT. The clinic attendance was very satisfactory in all cases (minimum 75%). The project average regularity is 77% over the whole control area.[3]

One of the patients received 12 doses of MB–MDT, possibly because his smear was initially 1+. Except for this patient, all patients were smear negative at their initial examination. Five patients received MT for a considerable length of time (15–52 months) before starting PB–MDT. However, this did not make any difference on the relapse interval. Only 2 patients were smear positive (1+) at the time of relapse.

In our study all relapses occurred within 4 years after release from treatment (RFT) and 92% even occurred within 3 years. But since the first patients were only released from (PB) MDT $4\frac{1}{2}$ years ago, there may still be a group of 'late' relapses, which so far have not been discovered.

* Body area is defined as follows: 1 area is the head, or 1 arm or 1 leg, or half of the front or back of the trunk, when divided in halves sagittally. The total number of body areas is therefore 9.

Table 4. Body areas involved

Type	<3	3–4	5–6	⩾7	Total
BT	—	3	4	9	16
BL	—	—	1	3	4
LL	—	—	1	1	2

Table 5. Relapse percentages

Classification	No. of patients RFT	No. of relapses	Relapse (%)	Annual (%)
PB	555	16	2·9	0·73
MB	372	6	1·6	0·4
Total	927	22	2·4	0·6

MULTIBACILLARY GROUP

In this group there were 6 relapses, 4 were classified 'BL' and 2 'LL' at their initial examination. All were smear positive, (2+–5+). All but one received DDS or Isoprodian therapy before starting MB–MDT. Again this, though shortening the length of MDT, did not affect the relapse interval.

Clinic attendance was again very satisfactory, though overall slightly less regular than in the PB group. The lowest percentage was 86%. The WHO standard is a minimum of 67%. Three patients were smear positive as a first sign of relapse. These were all found during routine annual follow-up examinations.

Discussion

We are aware of the difficulty in distinguishing relapse in PB patients from late reversal reaction. Waters *et al.*[4] discuss the problems in differentiating between the two, clinically, bacteriologically and histologically. Even the latter, '. . . may fail to distinguish between relapse and reversal reaction.' In practice, however, the great majority of diagnosis are made based on clinical judgement under field conditions. So we look for clinical criteria on which the diagnosis 'relapse' can be made with reasonable certainty. In only 1 out of our 22 patients did the lesions at the time of relapse look like reversal reaction.

We reckoned that this was not 'a late reaction,' but a relapse presenting as RR, because it occurred 41 months after RFT. It is possible for reactions to occur after RFT. This nearly always happens within the first year after starting chemotherapy, but occasionally can occur up to 3 years after the beginning of effective chemotherapy.[4] Some of our patients, who presented with symptoms of neuritis only, may have been reversal reactions, who showed no 'reactional skin lesions,' because they had no active skin lesions.

Among our 22 patients 6 had nerve problems only; the rest had either new skin lesions (usually hypopigmented macules) or they had a positive skin smear.

Relapse can have the following causes:

Original misclassification (leading to wrong treatment).

2 Inadequate chemotherapy due to: (a) low dose treatment; (b) treatment mistakes; (c) irregularity and non-compliance of the patient; and (d) inadequate treatment protocols.
3 Drug resistance.
4 *M. leprae* persisters.
5 Re-infection (only likely in lepromatous patients).

Causes 1–2(b) were excluded from our study, so cannot account for any of the relapses. Noncompliance is a widely recognized phenomenon. However, looking at the clinic attendance regularity, there is no reason to think that these 22 patients would be less compliant than nonrelapsing patients, Pandian *et al.* write:[5] 'This relapse rate does not appear to be related to the regularity of treatment.' The reason for this, they argue, is that the sulphone levels in the blood remain above the MIC for as long as 10 days after the last (100 mg) dose. Therefore even very irregular self-administration should still lead to adequate therapy. This is even more so if monthly supervised rifampicin is added to the treatment regimen.

Non-compliance with treatment is also more likely to lead to 'failure to cure' or relapse during treatment, than to relapse after RFT. All our relapse patients had previously responded favourably to MDT, indicating sufficient compliance. Since only the WHO–MDT protocols were used, we assumed that they had been given 'adequate treatment'. However, 'the ultimate and significant test of chemotherapeutic effectiveness is and will be the relapse rate'.[4]

Drug resistance as a cause for these relapses is very unlikely after a course of MDT, combining 3 effective antileprosy drugs. Re-infection remains a possible cause of relapse in lepromatous patients, because of their lasting defect in their cell-mediated immunity. Almeida *et al*, write:[6] 'In a leprosy-endemic area, it is argued that beyond the first 3 years of smear negativity in a LL or BL patient, sources of *M. leprae* outside the patient may be more responsible for relapse, than a patient's own bacilli. Since all our relapses in the MB group occurred within $2\frac{1}{2}$ years after RFT, re-infection is not likely to play a major role here.

The most likely explanation of the relapses in the MB group is persistence of *M. leprae* bacilli in the tissues. This has been reported by several investigators. These persisters are usually fully sensitive to the drugs used before. Therefore Toman[7] writes: 'There is little reason to believe that in the near future a new drug or combination of drugs will be found that is capable of eradicating persisting *M. leprae*.' Jopling[8] found that MDT is unable to eradicate persisters in about 7% of MB patients.

Concerning the 'relapse interval' or 'incubation time for relapse', our findings are in agreement with those of Bourland *et al.*[9] They found that 50% of the relapses occurred within 3 years after RFT. In our study this was even as much as 92%. The overall relapse percentage is 2·6%. The annual exam rate among 'RFT patients' is only $\pm 50\%$. But since most patients presented themselves with symptoms in between the annual exam dates, the relapse percentage found is assumed to be close to the actual percentage in the whole group of RFT patients.

An overall relapse percentage of 2·6% seems to indicate that the MDT regimens as recommended by WHO offer very acceptable and adequate treatment for the great majority of patients. However, we hope to find that by treating BT patients with more than 2 body areas involved with MB–MDT, that the relapse rate in this group will be even further reduced.

We would like to emphasize again the following points:

1 The need for regular, annual follow-up, in order to detect relapses as early as possible (in our programme: PB 4 years, MB 8 years).
2 The need to include skin smears as a routine procedure in the follow-up examination (especially in the case of MB patients).

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