Does clofazimine prevent Erythema Nodosum Leprosum (ENL) in leprosy? A retrospective study, comparing the experience of multibacillary patients receiving either 12 or 24 months WHO-MDT

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Summary

Objective: To compare the occurrence, duration and severity of ENL in leprosy patients treated with either 12 or 24 months of standard multi-drug therapy (MDT).

Materials and Methods: Study population: 296 patients treated with MDT for 2 years, between 1985 and 1992 and followed up as part of a relapse study; and 293 patients, treated between 1998 and 2004, with MDT for 1 year and also followed up as part of a relapse study. The Chi squared test and multiple logistic regression analysis were used to test for statistical significance.

Results: ENL was not significantly more common, but it was longer-lasting and more severe in patients receiving only 12 months of MDT, as compared with those receiving 24 months treatment. A high BI at the start of treatment significantly increased the risk of severe ENL by a factor of between 6 and 12, while treatment with 12 instead of 24 months of MDT significantly increased the risk by a factor of between 3 and 10.

Conclusions: This study provides further evidence that a high initial BI is the key risk factor for ENL. It also suggests that the difference between these two cohorts in their experience of ENL as demonstrated in this study, may be related to the different amounts of clofazimine which the two cohorts were given in the early years of their treatment. Further studies are needed to determine whether clofazimine could be used more specifically to reduce the severity of ENL in the small group of patients at high risk for the condition.

Introduction

Erythema Nodosum Leprosum (ENL), also known as Type II reaction, is a well recognised complication of leprosy, occurring exclusively in BL and LL patients.1 ENL has been
regarded as one of the most severe complications of the disease and although leprosy is not
generally associated with a high mortality, those deaths that did occur in earlier times were
often related to chronic ENL, secondary amyloidosis and renal failure. Steroids were
discovered at the start of the antibiotic era and in leprosy during the 1950s were used
exclusively to treat ENL; only later were they found to be useful in suppressing the
neuropathy associated with reversal reactions. Treatment is difficult because of the
potentially severe side-effects of the drugs currently available and the lack of good evidence
on which to base an effective therapeutic strategy. There is great interest in the search for
safer and more effective medication for this condition.

The pathology of ENL is poorly understood, involving immune complex deposition, as
well as a localised cell-mediated immune response with vasculitis. Levels of certain
cytokines, including TNF alpha and IL-6, have been shown to be consistently raised, while
others, such as IL-4 are low. While the clinical features are most obvious in the skin, ENL is
a systemic condition affecting many organs, including the eyes, joints and kidneys. An
important characteristic of ENL is its chronic nature. Even today, when the infecting
organism, *M. leprae*, is rapidly killed at the start of effective chemotherapy with bactericidal
drugs, the condition waxes and wanes for up to 5 years or more, in severe cases, eventually
resolving completely.

The management of ENL has changed very little in recent years. The suppressive effect of
clofazimine has been known for some time, while the two additional drugs used most widely
are prednisolone and thalidomide. Prednisolone is effective in controlling ENL, but side-
effects are a major problem in the more severe cases, which may need treatment at high doses
for several years. Thalidomide was initially thought to act through its anti-TNF alpha action,
but recent evidence suggests this is not the case, and the search continues for new drugs that
can mimic its potent anti-ENL effects while avoiding its well-known teratogenic side-effects,
which currently severely restrict its use.

Clofazimine is an orange-coloured imino-phenazine dye with a weakly bactericidal
action against *M. leprae*. Its mechanism of action is unknown and very few cases of drug
resistance have been reported. It is unevenly distributed throughout the body, but very
persistent in the tissues and, at high doses, may even precipitate out to form crystals,
especially in the intestinal mucosa, lymph nodes and fatty tissue.

The most common side effect is discolouration of the skin, with increased pigmentation,
although this gradually fades over a period of 1 to 2 years once the drug is discontinued. Different societies and social groups have differing degrees of tolerance of this problem. The formation of crystals in the gastrointestinal tract, may lead to abdominal pain, nausea and
diarrhoea, which may be fatal in severe cases.

Clofazimine has long been regarded as having a mild immuno-suppressive effect, beneficial in ENL reactions. This effect is not seen in Type I (or reversal) reactions. In severe, chronic cases of ENL, an increased dose is recommended, although care must be
taken to avoid the dose-related side-effects in the gastrointestinal tract. While clofazimine is
not adequate on its own in severe ENL, it may significantly reduce the requirement for
steroids. ENL is less frequent and less troublesome when patients are treated with a drug
regimen which includes clofazimine. The mechanism for this suppressive effect is
unknown.

Clofazimine is given orally as a daily dose of 50 mg; because of its long half-life in the
body, a monthly supervised dose of 300 mg was included in the WHO-recommended regimen
for multibacillary patients. The purpose of this was to try to provide some protection against
rifampicin monotherapy in patients who, for whatever reason, did not adhere correctly to the regimen and missed some or all of the unsupervised daily doses of dapsone and clofazimine. In severe ENL, clofazimine may be given in a dose of 300 mg daily for one month, followed by 200 mg daily for 5 months, followed by 100 mg daily indefinitely, while the condition persists.

Surprisingly, little attention has been paid to the prevention of ENL. It is generally regarded as an inevitable complication in a proportion of patients with a high bacillary load. At the Cebu Skin Clinic (CSC) in the Philippines, it was noted that ENL appeared to be more of a problem when the length of treatment with MDT was reduced from 24 months to 12 months for multibacillary cases, following the meeting of the WHO Seventh Expert Committee on Leprosy in 1998. We therefore decided to compare the experience of ENL in two cohorts of patients, given either 12 or 24 months of MDT, who had been recruited and rigorously followed up for relapse studies being conducted at the CSC.

**Materials and Methods**

A cohort of multibacillary patients had been recruited for a relapse study of 2 year MDT during the late 1980s and early 1990s, as described by Cellona *et al.* Although 316 subjects were originally recruited at the Cebu Skin Clinic, for the current study we excluded those lost to follow-up and those treated with additional MDT, usually because of relapse; thus 296 from that cohort are analysed here. A similar cohort of 293 patients was recruited between 1998 and 2003, to determine the relapse rate after 1 year’s MDT. Both cohorts were recruited at the Cebu Skin Clinic, using the same procedures, which included recruiting each consecutive eligible case who completed treatment correctly and who consented to participate in the long follow-up. Subjects were examined and actively followed up annually by the same clinicians under the leadership of one of the authors (MB), and were managed in the same way, apart from the length of MDT. Annual slit-skim smears were examined. The records of both cohorts were examined to extract details of ENL experienced by patients. The two MDT regimens were identical apart from the duration of treatment, and contained the following drugs (only the adult doses are given): rifampicin 600 mg monthly, clofazimine 50 mg daily and 300 mg monthly, dapsone 100 mg daily; the monthly doses were supervised and the daily doses were unsupervised.

When ENL was noted, it was graded as either mild or severe, according to clinical criteria which remained the same for both cohorts. This grading was done by clinicians at the time ENL was being diagnosed and managed and is recorded in the medical records; it is not a retrospective classification. Mild reactions were those with less than 20 papulonodules and no systemic signs; severe reactions were those with more than 20 papulonodules, or any of the following signs and symptoms: joint pains, constitutional symptoms, nerve involvement, oedema, or ulceration.

The duration of each episode of ENL was also noted in the medical record. For regression analysis, we used a duration of more than 20 weeks as another indicator of severity.

Thalidomide is not available for use in the Philippines, so patients were managed with prednisolone and in some cases, additional clofazimine. In general, the same management policies were applied to both cohorts. The use of additional clofazimine was determined by the severity of ENL and its response to steroid treatment.
Regarding treatment of ENL, mild cases received non-steroidal anti-inflammatory drugs. Steroids were only given in severe cases of ENL, particularly if reactions were associated with neuritis or if ENL lesions were located on the face. Prednisolone was given at 20–40 mg daily. A higher dose of 50 mg daily was given if ENL was associated with neuritis. Steroid doses were tapered every 2 weeks and adjusted according to weight, severity and clinical response to treatment. Clofazimine was only given if steroids could not be tapered below 20 mg daily after 12 weeks. Clofazimine was given at 200–300 mg daily for one month; 100–200 mg daily for the second month; 100 mg daily for the third month, and 50 mg daily until no ENL lesions were noted for 4 successive weeks.

As an additional measure of severity, the total dose of prednisolone prescribed to each patient with ENL was recorded in the medical records and was available for retrospective analysis. For the regression analysis, we used a total dose of $\geq 2$ gm as a marker of severity (a typical 12–week course of steroids which is widely used as a standard course, gives a total dose of 1.68 gm).

Four outcome indicators were examined: the occurrence of ENL and three measures of the severity of ENL, namely, the clinical assessment, the duration of symptoms and the total dose of prednisolone given. The data were analysed using Statcalc for the $\chi^2$ test for comparing proportions and Epi Info 3.4.3 for the multiple logistic regression analysis of risk factors.

**Results**

The two cohorts were recruited at different times, because the primary purpose of the studies was to examine the relapse rate following the MDT regimens currently recommended by WHO. The recommended duration was reduced from 24 months to 12 months in 1998. Table 1 shows the demographic and disease characteristics of the two cohorts.

Of the characteristics described in Table 1, the only significant difference between the two cohorts was the initial BI, the average of the BIs at all six sites taken at one time for the slit-skin smear test. The difference in the proportions with a BI of 4 or more, was 0.17 (95% CI: 0.09–0.25), indicating that the 1-year MDT cohort had a significantly higher bacillary load and thus an increased risk of ENL. For this reason, any comparison between the two groups must include a multivariate analysis.

Figure 1 shows the occurrence of the first episode of ENL during each year of follow-up. During the first year, while both cohorts received the same treatment, the results are not

<table>
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<tr>
<th>Table 1. Baseline characteristics of the two cohorts</th>
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<tr>
<td>Mean age in years (range)</td>
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<tr>
<td>Gender M:F</td>
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<tr>
<td>Initial average BI (mean)</td>
</tr>
<tr>
<td>Initial average BI (range)</td>
</tr>
<tr>
<td>Proportion with BI of 4 or more</td>
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<tr>
<td>Leprosy type</td>
</tr>
<tr>
<td>LL</td>
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<td>BL</td>
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significantly different. During the second year, when one group has stopped MDT, that group has a significantly greater number of subjects developing ENL \((p < 0.001)\) and also a significantly greater proportion getting severe, rather than mild ENL \((p < 0.005)\). In years 3 and 4, the same trend appears to be present, but as the numbers are much smaller, the differences are not statistically significant.

Table 2 shows three indicators of severity of ENL. Firstly, the clinical examination showing signs and symptoms meeting the criteria for severe disease; secondly, the duration in weeks of each episode was noted and summed to produce an overall total, so that for each person affected, the number of weeks with ENL was recorded; typically this would be the total for a number of distinct episodes added together, as the condition waxes and wanes over time. Thirdly, the total dose of prednisolone was recorded for each patient. In these cohorts, no cases in the 2 year MDT group received additional clofazimine whereas about 30% of the ENL cases in the 1 year MDT group received additional clofazimine (with steroids) to suppress ENL. Likewise, the total amount of steroid intake in each case was determined by both the severity and the total duration of ENL – that is, total steroid intake was significantly

**Table 2.** Characteristics of ENL reactions in each group

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<tr>
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<th>One year MDT</th>
<th>Two years MDT</th>
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<tr>
<td>Total number of cases with ENL</td>
<td>(N = 60)</td>
<td>(N = 36)</td>
</tr>
<tr>
<td>Clinical diagnosis of severe ENL: n (%)</td>
<td>55 (92%)</td>
<td>14 (39%)</td>
</tr>
<tr>
<td>Total duration of ENL in weeks:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>49.7</td>
<td>12.4</td>
</tr>
<tr>
<td>Range</td>
<td>8–125</td>
<td>3–44</td>
</tr>
<tr>
<td>Duration &gt;20 weeks: n (%)</td>
<td>48 (80%)</td>
<td>8 (22%)</td>
</tr>
<tr>
<td>Average number of episodes per patient</td>
<td>2.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Average duration of each episode</td>
<td>17 weeks</td>
<td>5–3 weeks</td>
</tr>
<tr>
<td>Total dose of prednisolone (gm) given:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>10.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Range</td>
<td>0.0–34.7</td>
<td>0.1–4.2</td>
</tr>
<tr>
<td>Cases given &gt;2 gm prednisolone: n (%)</td>
<td>51 (85%)</td>
<td>5 (14%)</td>
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**Figure 1.** The occurrence and severity of the first episode of ENL, over four years of follow-up. In this Figure, the terms mild and severe refer only to the clinical assessment.
higher in patients with more severe, prolonged or recurrent ENL, compared to those who had only mild, short term ENL, as was the case of most ENL patients in the two year MDT group.

Table 3 examines risk factors for all four outcomes (occurrence of ENL and three measures of severity), using multiple logistic regression analysis. Leprosy type (either BL or LL disease) is closely correlated with the initial BI, so we chose to use the latter for the analyses, which were therefore carried out using four independent variables – age, sex, the initial BI and the MDT regimen.

With the appearance of any episode of ENL as the outcome, the multivariate analysis showed that this difference is best explained by the difference in BI between the two groups. The different treatment regimens do not have a significant effect on the occurrence of ENL.
On the other hand, all three indicators of severity were significantly associated with both the initial BI and the treatment regimen given. For a person with a BI of 4 or more, the adjusted odds ratios were, for clinical severity, 5·5; for duration greater than 20 weeks, 11·8; and for total prednisolone dosage greater than 2 gm, 11·7. For a person treated with only 12 months MDT, the adjusted odds ratios were, for clinical severity, 3·9; for duration, 5·8; and for prednisolone dosage, 10·3.

We also looked at an aggregate measure of severity, combining all three individual measures, which produced adjusted odds ratios of 2·6 (95% CI: 1·5–4·5) for the 1 year MDT group and 6·1 (95% CI: 3·1–11·9) for the high BI subjects. In general therefore, a high BI at the start of treatment increased the risk of severe ENL by a factor of between 6 and 12, while treatment with 12 instead of 24 months of MDT increased the risk by a factor of between 3 and 10.

Regarding reversal reactions, the results were very similar in the two cohorts, year by year, although during the first year of treatment, the severity was significantly greater in the more recent (1 year) cohort, when the actual treatment being given (MDT) was exactly the same. This suggests that awareness of reactions on the part of both patients and health staff may have increased during the period between the recruitment of each cohort.

Discussion

Two cohorts of multibacillary patients were reviewed for their experience of ENL reactions. The study confirmed previous reports that a high initial BI is the most important risk factor for ENL. The two groups took different MDT regimens, and, although there was some difference in the initial BI of the two groups, the difference in the anti-leprosy treatment is associated with a significant difference in the severity of ENL experienced, although not in the proportion of subjects who experienced episodes of ENL. We have demonstrated that ENL was more commonly severe following 1 year rather than 2 year MDT. Whether this observation is a function of more prolonged MDT or clofazimine, the only component of MDT known to ameliorate established ENL, is unclear. In the treatment of ENL clofazimine at 300 mg daily is known to augment prednisone treatment and reduce the required prednisone dosage. In the WHO MDT regimen for MB leprosy, clofazimine is administered once monthly (supervised) in a dose of 300 mg and daily in a dose of 50 mg (unsupervised). Thus, if the clofazimine component of WHO MDT were the critical determinant resulting in less severe ENL as noted here following 2 year MDT, its prophylactic dose must be considerable lower than the dosage required to affect established ENL.

Clofazimine is unlikely to be included in new regimens because of its ability to kill M. leprae, as it is now surpassed by many newer drugs in this respect. We suggest, however, that clofazimine may play a role in suppressing ENL reactions in those patients with an initially high BI (an average BI of 4 or more). ENL remains amongst the most troublesome of the complications of leprosy and it would be unfortunate if it becomes more of a problem in future because clofazimine is no longer a component of the ‘best’ bactericidal regimens.

It should be noted that, although clofazimine is a very safe drug when used correctly, it is not easily available in some countries, because it is of limited use outside the field of leprosy. Thus, for example, it is difficult to prescribe clofazimine in the United States and some multibacillary patients there are being treated with alternative antibiotics (D. Scollard, personal communication). In other countries, including the Philippines,
clofazimine is available in the MDT blister-packs supplied by WHO, but is difficult to get as a single drug.

The study reported here has several deficiencies. It was retrospective and compared two different cohorts of patients, one of which had a significantly higher initial BI. The grading of severity took place before the development of severity scales for leprosy reactions and could therefore be regarded as somewhat subjective. The use of additional indicators of severity, however, including duration of ENL and the total dose of prednisolone prescribed, each of which gave essentially the same result, and the use of multiple logistic regression analysis, lend some confidence to the overall finding. However, it is clear that the general awareness of reactions has improved: patients may be more willing to complain of symptoms and staff may be more willing to take complaints seriously during the period in which the 1 year cohort was being treated.

In summary, this study suggests that an extended period of coverage with clofazimine may reduce the severity of ENL in the relatively small number of high risk patients, namely those with the most multibacillary form of leprosy (LL, or average initial BI of 4 or more). Further research is required to confirm this tentative finding and, if confirmed, to identify the best way of using clofazimine to minimize the effects of ENL.

Acknowledgements

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