Commentaries

The following article, on the use of thalidomide in the treatment of leprosy, appeared in the WHO Pharmaceuticals Newsletter, No. 2, 2003, and can be found on the WHO website (http://www.who.int/lep/TAG/Thal.doc). The article is followed by three commentaries on Dr Pannikar’s article, from Dr G. F. M. Pereira, of the Ministry of Health in Brazil, from Dr Diana Lockwood and Dr Anthony Bryceson, of LSHTM, London, UK, and from Ben Naafs, of Leiden University Medical Centre, Leiden, The Netherlands, Regional Dermatology Training Centre, Moshi, Tanzania and Instituto Lauro de Souza Lima (ILSL) Bauru SP, Brazil.

The return of thalidomide: new uses and renewed concerns

Dr V. Pannikar, Medical Officer, Communicable Diseases (Leprosy Group), WHO

History

Thalidomide or α-(N-phthalimido) glutarimide was marketed in 1957 for morning sickness and nausea and soon became the ‘drug of choice to help pregnant women’. It went into general use by the following year and was widely prescribed in Europe, Australia, Asia, Africa and the Americas. Allegedly, the drug was harmless and a lethal dose could not even be established. However, in the early 1960s, in what might be described as the worst case of pharmaceutical oversight, the drug was found to be associated with a congenital abnormality causing severe birth defects in children born of women who had been prescribed this drug during pregnancy. More than 10,000 cases of birth defects were reported in over 46 nations following thalidomide exposure. Children were born with missing (amelia) or abnormal (phocomelia) legs, arms, feet and hands; spinal cord defects; cleft lip or palate; absent or abnormal external ears; heart, kidney, and genital abnormalities; and abnormal formation of the digestive system. It is estimated that 40% of thalidomide victims died within a year of birth. Today there are approximately 5000 thalidomide survivors. The ‘thalidomide syndrome’ triggered a world wide response. Safety monitoring systems were set up to prevent this tragedy ever happening again and the drug was taken off the market in many countries in 1961.

Thalidomide in leprosy

A few years later, however, the drug thalidomide was reintroduced as treatment for a complication of leprosy called erythema nodosum leprosum (ENL). Although the evidence was not fully established, very soon the drug was heralded as the drug of choice for the management of ENL reactions in leprosy and regulatory authorities granted exemption from licensing requirements to enable doctors to obtain limited supplies of thalidomide under strictly controlled circumstances for use in named patients. Thalidomide’s effectiveness in minimizing symptoms of ENL was mainly due to its antipyretic action. Its effectiveness in controlling neuritis, the major cause of permanent disabilities in leprosy, was limited.

Several controlled studies done in the 70’s have demonstrated that prednisolone is more effective in
controlling ENL and associated neuritis.\textsuperscript{4–6} In addition, it was demonstrated that clofazimine, an anti-leprosy drug introduced on a small scale in the early 60’s had anti-inflammatory action.\textsuperscript{7,8} Studies showed that clofazimine is the drug of choice for the management of chronic, recurrent ENL reactions, as it had both anti-reaction and anti-leprosy effect. Moreover, while almost all patients given thalidomide relapsed after discontinuation of the drug, none of the patients treated with clofazimine for ENL reactions relapsed.\textsuperscript{9–11} The drug clofazimine is now a component of the multidrug therapy (MDT), introduced by WHO in 1981 as the standard treatment for leprosy. The presence of clofazimine in the combination has significantly reduced the frequency and severity of ENL reactions worldwide.\textsuperscript{12,13}

Today, ENL reaction is a rare complication, limited to a small proportion of multibacillary patients. Most of the ENL reactions are mild in nature and do not require any specific treatment except with some analgesics/antipyretics. In those suffering ENL associated neuritis, the drug of choice is prednisolone. For chronic recurrent reactions the drug of choice is clofazimine.

**Thalidomide in other indications**

The above points clearly demonstrate that there is no place for thalidomide in leprosy. But very often this disease is used as an entry point to reintroduce thalidomide for a multitude of other indications. Millions of treatments are being prescribed annually and almost all of it is for non-leprosy conditions including cancer treatment and use in HIV. There are limited trials demonstrating the efficacy of thalidomide in other conditions.\textsuperscript{14,15} Each condition must be evaluated in its own right and there must be put in place stringent restrictions on its availability. In addition there must be a monitoring system in place. There is no justification in extrapolating data from monitoring systems for leprosy to other conditions. The medical community that support the use of thalidomide for other conditions should make their own case for the drug. They cannot base it on the leprosy studies which are anything but exhaustive.

**In conclusion**

Today, a large number of thalidomide babies continue to be born each year\textsuperscript{16–18} possibly reflecting regulatory insufficiency and widespread use under inadequate supervision. In Brazil, which has more than 1000 registered thalidomide victims, the last officially known case was born in 1995.\textsuperscript{19,20} There is evidence that second generation babies with similar deformities are being born to thalidomide victims.\textsuperscript{21,22} In the US, Celgene Corporation has had FDA approval to market the drug since 1998 for the cutaneous manifestations of moderate to severe erythema nodosum leprosum. In Europe, the US company Pharmion Corp and French rival Laphal have both secured orphan drug status for thalidomide and have applied to market the drug as a therapy for multiple myeloma and for ENL in the EU. The EU is currently holding discussions on the re-launch of thalidomide. Whatever the outcome of the EU discussions, it cannot be over-emphasized that any potential benefit with thalidomide must be balanced with the known toxicity and the accompanying ethical and legal constraints on its use. Experience has shown that it is virtually impossible to develop and implement a fool-proof surveillance mechanism to combat misuse of thalidomide.

**References**

On thalidomide and WHO policies

Dr G. F. M. Pereira, Ministry of Health, Brazil

The Brazilian scientific community felt perplexed on reading the publication ‘The Return of Thalidomide: New Uses and Renewed Concerns’, by Dr V. Pannikar, Medical Officer, Communicable Diseases (Leprösy Group), WHO.

WHO is an intergovernmental organization and thus, in principle, its policies should be authenticated by the Member Countries as well as by the international scientific community. A review of its official publications shows that the debate on thalidomide (TH) was not included in any technical report of its expert committees in recent decades. This was quite natural, since Brazil was the only country manufacturing TH.

Denying the truth is avoiding its responsibilities. In the last decade, the use of TH as a potent modulator of the immune response has been recuperated. To say that its action on erythema nodosum leprosum (ENL) is only due to its antipyretic action is to ignore dozens of papers describing the action of TH on TNF-α, an important pro-inflammatory cytokine. It is also to ignore the possibility, already published in the literature, of obtaining TH analogues. If obtaining such analogues is not possible, the use of TH should be surrounded by all possible safeguards and carried out, since it is undoubtedly a promising drug in frank redemption. WHO should be reminded that there is no innocuous drug; every one, without exception, has side effects. It should also note that the second-line options for treating patients with ENL are steroids and clofazimine, but the many severe and unesthetic side effects of both drugs were not mentioned by Dr Pannikar.

Has WHO forgotten how difficult it is to fight a stigma, like the stigma of leprosy or the stigma of AIDS? Is WHO now planting the seeds of another stigma?
What is WHO’s experience with TH alone, and with TH in ENL? The literature shows a single mention that WHO sponsored a comparative study between TH and AAS in the 1960s, with results favourable to TH.

Why was this recent publication issued without the customary consultation to the scientific community and to governments with experience on the issue?

Specifically concerning Brazil, the scientific data presented therein are wrong. ‘In Brazil, which has more than 1000 thalidomide victims ( . . . )’. Where did this information come from? There have been only 56 reported TH accidents in Brazil in the last 4 decades.

The literature also shows that after 1965, only Brazil continued to manufacture TH in a commercial scale, for the purpose of supplying the Brazilian Leprosy Control Program. Perhaps it was also produced in other countries and used in research, although its manufacture was forbidden in these countries.

Since 1965, 637,848 new leprosy cases have been registered in Brazil for treatment, of which 303,230 were MB cases. Approximately 30% of them (90,969) had type 2 reactions (ENL) and received thalidomide. This is the largest Brazilian experience with the drug, which has also been used in much smaller volume for other conditions.

In the last 5 years (1998–2002), the Brazilian Ministry of Health purchased 18 million capsules of thalidomide and 54 million tablets of steroids (prednison 5 and 20 mg) for the treatment of reversal lepra reaction.

A large study sponsored by the Brazilian Society of Dermatology in cooperation with the National Agency for Sanitary Surveillance (ANVISA/MoH) carried out in 2001 resulted in broadening the therapeutic use of thalidomide for other diseases beyond ENL, under strict surveillance, and allowing its use in women of childbearing age, under supervision of the Brazilian Federation of Gynecology and Obstetrics (FEBRASGO).

The conclusion of the WHO document that ‘Experience has shown that is virtually impossible to develop and implement a fool-proof surveillance mechanism to combat misuse of thalidomide’ proves another lack of knowledge on the enormous development in the field of pharmacological surveillance in France, the USA and Brazil, not only on TH but on many other drugs, teratogenic or not. Indeed, without pharmacological surveillance there would be no restricted black-label drugs.

Finally, we believe that WHO technical policies should be support by The Leprosy Expert Committee on Leprosy, so that, based on concrete evidence and supported by the scientific community, its positions continue to maintain the historical credibility of its recommendations, which (currently) lack, at least in the case of leprosy, soundness under the scientific knowledge.

**Further reading**


Moraes MO, Dupre NC, Suffys PN et al. Tumor necrosis factor-α promoter polymorphism (TNF2) is associated with a stronger delayed-type hypersensitivity reaction in the skin of borderline tuberculoid leprosy patients. Immunogenetics, 2001; 53: 45–47.
Commentaries


The return of thalidomide: new uses and renewed concerns—reply

Dr Diana Lockwood and Dr Anthony Bryceson, London School of Hygiene and Tropical Medicine, London, UK

Dr Pannikar1 draws attention to the growing interest in the use of thalidomide for conditions other than type 2 (erythema nodosum leprosum, ENL) reactions in leprosy, and rightly points out the dangers attendant upon the uncontrolled distribution of this teratogenic drug. But in doing so, he denies the place of thalidomide in the management of patients with leprosy. His statement ‘there is no place for thalidomide in leprosy’, goes against high quality data from randomized controlled trials and many uncontrolled studies published in peer-reviewed journals and the experience of practising leprologists, and contradicts the recommendations in the seventh report of the WHO Expert Committee on Leprosy.2

The problem of ENL

ENL is still common and serious. It occurs in patients with multibacillary, especially lepromatous (LL), disease, whose bacillary index may fall by about one log count each year in response to multidrug therapy (MDT), and whose antigen load, capable of triggering hypersensitivity responses, may remain

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in tissues even longer. ENL commonly persists or recurs over many years. ENL is a systemic illness with fever, weight loss and pain as well as a cause of damage to nerves, skin, eyes and testes etc. Levy\textsuperscript{3} found that ENL ‘produces greater disability than the underlying lepromatous leprosy, and . . . was the commonest reason for admission to hospital’. In Brazil, for example, of 162 newly diagnosed multi-bacillary patients 43 developed ENL during their 24 month course of MDT,\textsuperscript{4} accounting for 91% of reactions in lepromatous patients. In North East Thailand, 26% of lepromatous patients developed ENL during treatment,\textsuperscript{5} and in Nepal 6% of all leprosy patients developed ENL over a mean 21 months, and over half over them developed new nerve function impairment.\textsuperscript{6} Management of ENL demands a drug that can be used safely for many years. In this context, thalidomide, which is rapidly excreted, has limited toxicity and does not accumulate in the body, is more suitable than corticosteroids or clofazimine.

The efficacy of thalidomide

This has been clearly demonstrated in four randomized controlled trials (Table 1). Three were placebo controlled and patients with ENL showed clear clinical improvement whilst on thalidomide.\textsuperscript{7–9} The fourth study,\textsuperscript{10} a WHO multicentre study, compared thalidomide against aspirin. This drug was carefully chosen, since it is an antipyretic and thus the study should demonstrate the clinical improvement over and above the antipyretic and analgesic effect of aspirin. In this study, skin lesions improved and resolved more quickly with thalidomide, as did nerve lesions and other organ involvement (e.g. eyes, testes, lymph nodes). There are also numerous uncontrolled case series reporting on the efficacy of thalidomide.\textsuperscript{11,12,13} Patients maintained on thalidomide do not get further episodes on ENL.\textsuperscript{3,14}

Thalidomide and nerve damage

The available evidence suggests that in ENL reactions, thalidomide controls neuritis, relieves pain and improves nerve function,\textsuperscript{10,13,16,17,18} and if maintained prevents further episodes of neuritis.\textsuperscript{19} In Iyer’s multi-centre controlled study nerve lesions improved more rapidly on thalidomide.\textsuperscript{10} Sheskin et al.\textsuperscript{7,19} showed from motor conduction studies on six patients that both prednisolone and thalidomide improved nerve function during reaction, thalidomide more than prednisolone whilst the nerve function of patients on placebo or analgesics worsened. A 6-year neurophysiological follow-up of ulnar nerve function confirmed the finding.\textsuperscript{20}

Steroids versus thalidomide in ENL

It is disingenuous of Dr Pannikar to cite two non-peer reviewed book chapters and a WHO strategy document in support of his contention that prednisolone is more effective than thalidomide in controlling ENL. We could find no controlled studies directly comparing the two agents. A recent non-blinded comparison of pentoxifylline, thalidomide and prednisone in 16 patients with ENL showed that thalidomide gave the fastest and most effective clinical response.\textsuperscript{21} Earlier uncontrolled studies stress that thalidomide works faster than corticosteroids.\textsuperscript{10} Corticosteroids have distressing and disabling adverse effects, including dependency, in leprosy patients treated for reactions, especially type 2 reactions because of their long duration.\textsuperscript{22} Thalidomide may be used to wean patients off long-term steroids, with or without the addition of clofazimine.\textsuperscript{23,24} Patients with ENL who are already taking corticosteroids respond more slowly to thalidomide than do naive patients.

Clofazimine and ENL

There is no doubt that clofazimine is useful in the prevention and management of ENL.\textsuperscript{25} In one Indian study, 15 of 20 patients were free of reaction after 3 months, and five improved,\textsuperscript{26} while in another, 22 of


**Table 1.** Double blind controlled trials of thalidomide in type 2 leprosy reactions. Table adapted from Teo et al.\textsuperscript{12}

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial site</th>
<th>Design</th>
<th>Subjects</th>
<th>Dose (mg/day)</th>
<th>Duration</th>
<th>Clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheskin &amp; Convit\textsuperscript{2}</td>
<td>Venezuela</td>
<td>Double blind placebo control; crossover</td>
<td>52 (15 F)</td>
<td>400</td>
<td>7 days</td>
<td>Improvement in 78 of 85 (92%) thalidomide and only 24 of 88 (27%) placebo courses</td>
</tr>
<tr>
<td>Pearson &amp; Vedagiri\textsuperscript{4}</td>
<td>Malaysia</td>
<td>Double blind active control; crossover</td>
<td>12 (1 F)</td>
<td>300</td>
<td>4–6 weeks</td>
<td>Thalidomide decreased severity of ENL and requirements for steroids</td>
</tr>
<tr>
<td>Waters\textsuperscript{9}</td>
<td>Malaysia</td>
<td>Double blind placebo control; crossover</td>
<td>10</td>
<td>300</td>
<td>6 weeks</td>
<td>Patients taking thalidomide required 60% less steroids; temperature and severity of ENL also less</td>
</tr>
<tr>
<td>Iyer et al.\textsuperscript{10}</td>
<td>India, Mali, Somalia, Spain</td>
<td>Double blind active control; (aspirin)</td>
<td>92 M</td>
<td>400</td>
<td>7 days</td>
<td>After 2 days, only 25% of thalidomide-treated patients had fever; 65% aspirin-treated patients had fever. Thalidomide was more efficacious in regressing skin lesions</td>
</tr>
</tbody>
</table>

30 responded.\textsuperscript{27} The 7th WHO Expert Committee pointed out that it may take 4–6 weeks before clofazamine becomes effective, and that it should not be started on its own in severe reactions.\textsuperscript{2} Dyspigmentation in pale skins, and abdominal pain may limit its use over long periods.\textsuperscript{28,29}

**Thalidomide side effects**

Thalidomide has well recognized side-effects.\textsuperscript{12} Drowsiness, rash and constipation are not serious. Peripheral neuropathy has rarely if ever been noted in patients with leprosy, but in other conditions rates may exceed 20%. The cause of this differential toxicity is not understood. Teratogenicity is the important problem, for which reason it should not be prescribed for women of childbearing age. However, the danger of these side effects has to be balanced against the utility of this drug in treating a distressing and disabling condition that can extend over many years.

**The future of thalidomide**

While we share Dr Pannikar’s concern over the uncontrolled distribution of thalidomide in its wider application outside the field of leprosy, we find it difficult to understand why the WHO leprosy unit should downplay the seriousness of reactions in leprosy, ignore the scientific evidence of the value of thalidomide and attempt to deny leprosy patients such a valuable drug. The United States STEPS Program (System for Thalidomide Education and Prescribing Safety), designed to regulate the use of thalidomide has shown that this drug can be used safely and pregnancy avoided if there is co-operation
between governments and the pharmaceutical industry. In the field of leprosy thalidomide is not and would not be available at primary health centres, but should be available to trained staff at all referral centres. We would urge the WHO leprosy unit to take the lead in ensuring that thalidomide is available to those leprosy patients who need it, as recommended by the Expert Committee.

References

The return of thalidomide: new uses and renewed concerns—reply

Ben Naafs, Leiden University Medical Centre, Leiden, The Netherlands, Regional Dermatology Training Centre, Moshi, Tanzania and Instituto Lauro de Souza Lima (ILSL) Bairu SP, Brazil

When I read Dr. Pannikar’s article, ‘The return of thalidomide: new uses and renewed concerns’, I suddenly understood why the EU committee was so reluctant to follow my advice, through the Dutch representative, to register thalidomide, though under restriction. She told me that the WHO, in the person of Dr Pannikar, had given negative advice on the use of thalidomide in ENL. At that time I did not believe it, because as far as I knew of Dr Pannikar’s background, he had little hands-on experience with thalidomide. But ‘soil’ because it would involve politics I left it. However, since Dr. Pannikar’s paper, which I had not seen before, came under attack by Dr Gerson Fernando Mendes Pereira, who in rightful anger exposed himself to critics, I would like to comment.

Dr Pannikar has written a paper as a WHO leprosy representative and that gives the paper a lot of weight, which according to me it does not deserve. Being a WHO paper, I would expect it to be properly researched, which it certainly is not. The tone is demagogic and it contains a number of inaccurate statements.

Thalidomide was marketed as a sleeping pill, but when it was on the market it was found to have a pronounced effect on morning sickness and, since it seemed to be safe, it became widely prescribed. The history, as written by Dr Pannikar, is well known and it is mentioned rightly in most of the papers on thalidomide. We should never forget that Dr Lenz’ book, which is in Dr Pannikar’s reference list, describes it vividly and teaches us a lesson. This should never happen again, but that applies for all treatments and medications. However it does not imply that thalidomide has no place in medicine.

Dr Pannikar’s paper is a political paper and probably an emotional one (at least I hope so, otherwise I do not understand it at all), but it lacks scientific support. Twenty-five percent of his references are not free from those sentiments and were not written as scientific papers should be. Sixty percent of the quoted references are from 30 years ago, when dapsone monotherapy was still in use and dapsone resistance with relapses and consequent reactions was common. They are papers that would not pass the present criteria for scientific evidence. That certainly does not mean that the studies are not carefully done and that the observations are not sound, but that the data should be interpreted in the context of present knowledge.

What he clearly states is, that ‘there is no place for thalidomide in leprosy’. I wonder: are all the other leprologists wrong? On an e-mail-based leprosy discussion group, in response to a question on the treatment of ENL, I read seven responses by senior leprologists, all certainly familiar with the data on which Dr Pannikar based his ‘no place for thalidomide’. Six of them mention thalidomide, some quite strongly and one even asked that it should be made available! Some of them warn against steroids, which are, for Dr Pannikar, a main treatment option.

I fully agree with Dr Gerson that Dr Pannikar’s claim, ‘that the activity of thalidomide against ENL is mainly due to its antipyretic action’, is not based on a thorough study of the literature. Though much is still unknown, a simple PubMed search produces quite a number of review articles on its action (e.g. Meierhofer et al., Biodrugs, 2001; 15: 681). It is clear that the antipyretic action is only an epiphenomenon. The actual action is much more complicated, and points to immunomodulating properties. This is what makes the drug so fascinating!

Dr Pannikar states, defending alternative drug regimens, that ‘controlled studies have been done, showing that prednisolone is more effective in controlling ENL and associated neuritis’. He quotes, to underline his point, two books, which were written 25 years ago, and a policy document. But he does not
mention an internally controlled clinical trial that was favourable for thalidomide. (Waters et al., Lepr Rev, 1971; 42: 167). However, the problem is that, over the years, very few controlled studies have been done on the treatment of ENL and for that matter on all leprosy reactions (conclusion of a working group on reactions at the World leprosy congress in Beijing, 1998). From our own research and based on our own experience with thalidomide and prednisolone, I agree with him that at the initial period of treatment of an ENL neuritis, prednisolone, due to its strong anti-oedema action, is more effective than thalidomide. But I doubt whether it is still the drug of choice after that period and for other manifestations of ENL, which can be a multi-organ disease. Side-effects of steroid treatment in chronic and recurrent ENL are frequently encountered, while, nevertheless, permanent damage ensues. Some warn strongly against it. For many it is the reason to look for alternative treatments.

Dr Pannikar proposes clofazimine for this purpose. He even calls it the drug of choice. Most leprologists will agree that it has certainly a place in the treatment of ENL, but others who have access to thalidomide, Dr Dilip Oprimolla for instance, have strong doubts. Dr Pannikar defends the use of clofazimine with observations made in the mid-1960s that clofazimine had an anti-inflammatory effect. Again, it was the time of dapsone mono-therapy and resistance, the latter being responsible for bacterial multiplication. Treatment with clofazimine took care of this multiplication induced ENL (Burke et al., Lepr Ind, 1983; 55: 256), but was this due to its anti-inflammatory action or to its anti-mycobacterial activity? Having recently reviewed available data, in preparation for a manuscript together with Dr Pieter Schreuder, I agree that clofazimine may have some suppressing effect on ENL. But it takes time to establish, and one wonders whether we are looking at the normal course of the disease or at an effect of treatment. Only a controlled trial can solve this dilemma.

I have to agree with Dr Pannikar that the introduction of MDT has diminished the number of ENL reactions compared with monotherapy (Post et al., Ned Tijdschr Geneesk, 1994; 138). However, after the cessation of MDT, the reaction may still appear. I fully disagree that since the introduction of MDT, ENL is a rare complication. Depending on the accuracy of the data and the effectiveness of the programme in the early detection of leprosy, together with regional differences, which are as yet unexplained, still some 10–60% of the lepromatous patients develop ENL. I would not call that rare! The observation that ENL does not reappear after clofazimine treatment is due to a bias, because ENL is treated with clofazimine till everything is under control, which can be for months. Only later is it discontinued. When steroids and/or thalidomide are given for the same period, the reaction will neither re-appear. It has been shown that thalidomide is a perfect inhibitor of ENL. (Kaplan G, Lepr Rev, 2000; 71: S120.)

In the section on thalidomide for other conditions, Dr Pannikar is more careful, although he is off the mark when he claims that there are only limited trials demonstrating the effectiveness of thalidomide in conditions other than leprosy. A simple PubMed search will result in more than 1000 papers. I used thalidomide with success in a number of conditions (Naafs and Faber, Int J Dermatol, 1985; 24: 131) for 25 years. It is, however, no panacea.

I naturally fully agree that a proper monitoring system should be in use and that adequate measures should be taken to prevent pregnancy. That is evident. But nevertheless, it should not be forgotten that thalidomide, by itself, may cause nerve damage (Naafs and Faber, Int J Dermatol, 1985; 24: 131). This should be controlled too. Nerve damage may also be induced when thalidomide is used in leprosy (Naafs, unpublished observation).

In conclusion, I feel he oversteps evidence again, by suggesting that a large number of thalidomide babies are born each year. Other drugs (retinoids, cocaine, traditional medicines) and genetic conditions can results in similar abnormalities to those caused by thalidomide. Not every amelia or phocomelia is due to thalidomide.

Last, but not least, Dr Pannikar seems to have forgotten what he wrote earlier with Dr Noordeen in the famous Manson’s Tropical Diseases edited by Gordon C. Cook (1996), (Chapter 58, pages 1016–1044). Just two citations: ‘The main therapeutic weapons in the treatment of reactional states are steroids, clofazimine and, where not contra-indicated, thalidomide’, and ‘Thalidomide is also an effective drug in the treatment of ENL reaction’.