

# Are Guidelines for Field Treatment of Leprosy Reactions Evidence-Based? A Comprehensive Literature Review

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**Abstract: Purpose:** Much of the stigma associated with leprosy is caused by disfiguring disabilities following irreversible nerve damage and much of this damage is the end result of leprosy reactions which are either not recognized in early enough stages, not treated appropriately or both.

In an effort to improve access to care, to reduce stigma and to integrate leprosy into general health care services, guidelines for standardized treatment in field conditions of the infection itself and of leprosy reactions have been developed and implemented. This has sparked debate among experts concerning the efficacy of treatment protocols for especially leprosy reactions outlined in the guidelines. The principle points of contention are the duration of treatment, dosage and tapering strategies of the drug mainly used, prednisolone. This study investigates on what evidence these guidelines are based.

**Methods:** Electronic databases were used in search of randomized controlled trials and other non-randomized evidence that could shed light on the validity of the strategies advocated and already implemented in most leprosy control programs worldwide.

**Results:** Randomized controlled trials were found only for reversal reactions (type 1 reaction), and it could be concluded that the current strategies for field treatment of this type of reaction are not efficacious and do not yield better results than placebos. Instead, indications are that longer and higher dosed treatment strategies are needed to yield better results and this is supported by other non-randomized evidence.

**Conclusions:** Further randomized controlled trials are needed to determine optimal dosages, tapering strategies and duration of treatment. Non-randomized evidence suggests that the protocols are not optimal for type 2 reactions either and may need to be reviewed based on further research.

An outline for a randomized controlled trial is presented in an effort to further provide evidence for optimal treatment strategies for field treatment of type 1 leprosy reactions.

**Keywords:** Leprosy, leprosy reactions, treatment, comprehensive literature review.

## INTRODUCTION

The number of registered leprosy patients (new and already known) dropped from 5 million in 1985 to 0.7 million in 2001 [1]. At the beginning of 2008, WHO reported a global registered prevalence of leprosy of 212,802 cases and an incidence of 254,525 cases [2]. Only three countries (Brazil, Nepal and Timor-Leste) still report prevalence figures above the target of one per 10.000 population [2]. Mathematical modeling studies indicate that the current elimination strategy reduces transmission slowly, with 5 million new cases predicted to arise globally between 2000 and 2020 [3]. Assuming that a substantial proportion of these cases are in danger of developing neurological complications caused by leprosy reactions even when diagnosed and treated promptly with multidrug treatment (MDT), the relevance of clear, evidence-based guidelines for the treatment of leprosy reactions cannot be questioned.

Two important types of nerve damaging reactions can be distinguished. In borderline leprosy, nerve damage usually develops during a **type I** or **reversal reaction (RR)**. RR is a delayed-type hypersensitivity reaction (type IV Gell and Coombs) [4] directed against an increasing amount of *M. leprae* antigens, either due to multiplication of *M. leprae* or due to a breakdown of dead and dying bacilli within nerves. It is seen in borderline leprosy patients because they are able to develop cell-mediated immunity towards *M. leprae* antigens. Commencement of MDT sometimes triggers this type of reaction, but it is by no means uncommon to observe RR after MDT has been completed. In lepromatous leprosy, nerve damage usually develops more insidiously over many years but may suddenly increase in severity during a **type II** reaction, also known as **erythema nodosum leprosum (ENL)**. ENL is probably an immune complex-mediated (type III Gell and Coombs) [4] reaction and is less well understood than RR. It is usually a serious systemic condition with fever, weight loss and generalized pain [5].

Leprosy infection is treated with either 6 months or 12 months of MDT, depending on (the new WHO) classification as paucibacillary (PB) or multibacillary (MB) leprosy at

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the time of diagnosis. These are fixed treatment regimens and provided free of charge in blister packs to all in need.

The treatment of leprosy reactions is a source of much debate. For severe RR it is generally accepted that prednisolone is the drug of choice because of its dual action of suppressing the cell mediated immunity and reducing the inflammatory response, thereby decreasing intraneural pressure. The debate rises, however, when duration, dosages and tapering strategies are considered. When a lot of emphasis started being directed at integrating leprosy into general health care services in an effort to de-stigmatize the disease, the individually tailored approach with frequent monitoring of nerve function was no longer feasible “in the field” and fixed, standardized treatment schedules needed to be implemented.

For severe ENL, there is some debate whether or not thalidomide should be (re-)introduced as the drug of choice because of its superior effectiveness when compared to prednisolone [6]. However, because of restrictive political legislation in most countries due to fears concerning its teratogenicity, prednisolone is also considered the (second best-) drug of choice for ENL. Also for ENL there is debate concerning duration of therapy, optimal dosages and tapering strategies. More so than in RR, where duration of therapy seems to be the main point of debate, the question rises whether treatment strategies for ENL can be standardized at all because of its episodic and (sometimes chronically-) recurring nature.

In 2002, despite these considerations and in an effort to standardize reaction treatment, WHO recommended a standard treatment (in field conditions) of 3 to 4-months for both type I and type II reaction using blister packs (Prednipack®) as summarized in Table 1 [7].

**Table 1. Ambulatory Treatment of Leprosy Reactions with Prednisolone**

Period	Daily Dose (Not exceeding 1 mg per kg body weight)
Week 1 and 2	40 mg
Week 3 and 4	30 mg
Week 5 and 6	20 mg
Week 7 and 8	15 mg
Week 9 and 10	10 mg
Week 11 and 12	5 mg
Total 12 weeks	STOP

In the same document [7] thalidomide is not seen as an option for the treatment of ENL. For severe ENL, the recommendation is that “management... is best undertaken by physician at a referral centre” and “the dose and duration of anti-reaction drug treatment may be adjusted by the physician according to the needs of the individual patient”. Nevertheless, the standard 12-week prednisolone regimen is recommended as the first choice. Regarding the use of thalidomide, the document states that “...patients who require thalidomide for complicated ENL-type reactions are

very rare: in practice, most patients with leprosy reactions can be successfully managed by the proper use of other available anti-reaction drugs.” Whether or not this statement is backed up by evidence can not be assessed as no references are listed.

In a later document [8] the statements made in 2002 are partially superseded by now stating that a course of steroids “usually lasts 3-6 months”, that a leprosy reaction should be managed in a referral centre and that “other drugs may be needed for the treatment of ENL”. The problem here is that in a lot of endemic countries, referral centres are not available or only reachable at great cost to the patient. Health workers therefore still often rely on the previously recommended 12-week prednisolone regimen for lack of a better alternative guideline for standardized treatment.

While it is fair to assume that a standardized treatment can never be perfect for every single individual who experiences a leprosy reaction, it is also fair to assume that a majority of those patients will be treated adequately, without serious side-effects and with acceptable long-term results. It having been a WHO guideline, and thus still guiding policy in many leprosy endemic countries, it can be expected to be based on sufficient evidence.

The primary objective of this study is to investigate whether or not there is sufficient valid evidence to back up current field treatment guidelines for leprosy reactions. A secondary objective is to formulate possible recommendations for further research.

**METHODS**

A literature search was conducted in the Cochrane Database of Systematic Reviews and in MEDLINE, with a time frame of 18 years (1990 – June, 2008) as it was approximately in 1990 that WHO implemented leprosy (treatment) guidelines on a large and global scale. Final inclusion of studies was based on the following methodological quality criteria: concealment of allocation; blinding of participants and outcome assessors; loss to follow-up; clear diagnosis; baseline differences and explicit outcome measures mentioned.

**RESULTS**

A search in the Cochrane Database using the key words “leprosy” and “evidence” in “Title, Abstract or Keywords” yielded one result [9] out of 5053 records. A search in MEDLINE (PubMed) using “Leprosy/ drug therapy”[MeSH] OR “Leprosy/therapy”[MeSH] AND Limits: Publication date from 1990-2008 yielded 87 articles.

The articles were reviewed for relevancy regarding evidence-based medicine and leprosy in a broader sense (this yielded eight articles) and the relation between evidence-based medicine and leprosy reactions in a narrower sense (two articles) [1, 4]. Reference lists of these two articles were subsequently checked where relevant. Replacement of the key words “drug therapy” and “therapy” with the key words “clinical management”, “management”, or “treatment” yielded nil results.

The Cochrane review later served as a basis for a paper published in December 2008 [10].

### The Randomized Evidence

When assessing the Cochrane review [9], the main criterion for inclusion of studies in the review was any randomized controlled trial and quasi-randomized controlled trial involving corticosteroid treatment for nerve damage in leprosy.

Table 2 summarizes the most important characteristics of the trials included in the Cochrane review. The three trials included in the review all deal with corticosteroid regimens for type I reactions. Apparently none were found dealing with type II reactions. None, that is, that could qualify for inclusion based on the rigid criteria set out by the authors of the review. Since the search process was elaborate and included searches as far back as 1966, it is fair to assume that indeed none exist.

The three trials [11-13] ultimately included in the review involved a total of 513 patients. Two trials compared prednisolone with placebo, while the third compared three corticosteroid regimens for severe type I reactions. Importantly, none of the trials reported significantly higher numbers of serious adverse effects such as diabetes or peptic ulcer in the steroid groups when compared to the placebo groups. In the placebo-controlled trials, one treated mild sensory impairment of less than six months duration, while the other treated nerve function impairment of 6 to 24 months duration. Both trials used 16-week interventions with a starting prednisolone dose of 40mg/day, gradually tapered with 5mg/2weeks until 16 weeks were completed (4 weeks longer than the WHO-recommended regimen). Both examined the effect on nerve function improvement twelve months after the start of treatment. No significant difference

in nerve function improvement was found between patients treated with prednisolone or with placebo. However, the trial with the mild sensory impairment group found that the proportion of patients with sensory improvement in the prednisolone group was significantly higher than in the placebo group after four months. Unfortunately this difference disappeared by the six-month follow-up point.

In the third trial, a (short) 3-month course of prednisolone was compared with (longer) 5-month, low-dosed and 5-month, high-dosed courses, the primary endpoint being the need for additional corticosteroids during the 12-month trial period. A significantly lower number of patients receiving the longer prednisolone courses required extra corticosteroids. However, the effect of different steroid regimens on nerve function improvement was not evaluated in this trial, thus making comparison with the two placebo-controlled trials unsuitable.

Table 3 summarizes the interventions (prednisolone starting dose and tapering strategy) for each of the Cochrane review trials.

### The Non-Randomized Evidence

The duration and severity of nerve function impairment before the start of treatment seems to be of paramount importance. Van Brakel and Khawas [14] found significantly higher proportions of patients with moderate sensory impairment or moderate motor impairment improving to good function three months after the start of steroid treatment compared to those with complete anesthesia or motor paralysis. Becx-Bleumink *et al.* [15] and Britton [16] found that the recovery of nerve function loss is more likely when the duration of nerve function impairment is less than six months before the start of treatment. In a study in Ethiopia, Saunderson *et al.* [17] found that 88% of patients

**Table 2. Summary of Characteristics of Three RCT's Included in Cochrane Review**

Study	Methods	Participants	Intervention	Outcome	Main Findings
Sundar Rao (2006)	Randomized, parallel group trial Externally controlled computer randomization Double blind	334 patients with severe type I reactions	1. High-dosed prednisolone start with 5-month period to completion 2. Low-dosed prednisolone start with 5-month period to completion 3. High-dosed prednisolone start with 3-month period to completion	Additional requirement for corticosteroids for a 12-month trial period	Significantly more patients in the 3-month group required extra corticosteroids than the two 5-month groups
Van Brakel (2003)	Randomized, parallel group trial Externally controlled computer randomization Double blind Placebo-controlled	84 MB leprosy patients with sensory nerve impairment of less than 6 months duration	1. Prednisolone starting at 40mg/day and tapered in 16 weeks 2. Placebo, with same number of tablets for 16 weeks	Sensory score after 1 year using monofilaments Occurrence of major adverse effects	Initial significant improvement in the prednisolone group (at 4 months), but: No significant difference in nerve function improvement between prednisolone and placebo groups after 1 year No significant difference
Richardus (2003)	Randomized, parallel group trial Externally controlled computer randomization Double blind Placebo-controlled	95 MB leprosy patients with untreated sensory or motor nerve impairment of more than 6 months duration	1. Prednisolone starting at 40mg/day and tapered in 16 weeks 2. Placebo, with same number of tablets for 16 weeks	Sensory score after 1 year using monofilaments VMT score after 1 year using MRC five-point scale Occurrence of major adverse effects	No significant difference in nerve function improvement between prednisolone and placebo groups No significant difference

**Table 3. Prednisolone Starting Doses and Tapering Strategies for RCT's**

Period	Sundar Rao Regimen 1 (Long, High Arm)	Sundar Rao Regimen 2 (Long, Low Arm)	Sundar Rao Regimen 3 (Short, High Arm)	Richardus	Van Brakel
	Daily Dose	Daily Dose	Daily Dose	Daily Dose	Daily Dose
Week 1 and 2	60mg	30mg	60mg	40mg	40mg
Week 3 and 4	50mg	25mg	50mg	35mg	35mg
Week 5 and 6	40mg	20mg	40mg	30mg	30mg
Week 7 and 8	30mg	20mg	30mg	25mg	25mg
Week 9 and 10	20mg	20mg	20mg	20mg	20mg
Week 11 and 12	20mg	20mg	10mg	15mg	15mg
Week 13 and 14	10mg	10mg	placebo	10mg	10mg
Week 15 and 16	10mg	10mg	placebo	5mg	5mg
Week 17 and 18	5mg	5mg	placebo	STOP	STOP
Week 19 and 20	5mg	5mg	placebo		
	STOP	STOP	STOP		

with nerve impairment < 6 months had full recovery up to ten years after treatment with steroids as opposed to 51% of patients with > 6 months nerve impairment. These findings seem to back up the results of the randomized controlled trial (RCT) [13] with the group of patients with mild sensory impairments.

In the late 1970's, Naafs *et al.* [18] found evidence in favor of prolonged steroid treatment in a retrospective study comparing the benefits of short (two months) and long (three to eighteen months) steroid treatment for RR in borderline leprosy patients. In the long-term group, the starting dose was 30-40 mg once daily for one month, followed by a reduction of 5 mg every month. Importantly, "the dose was increased to the previous dose when nerve function parameters deteriorated, or when improvement came to a halt after dose reduction. A dose of 15-20 mg was the critical dose of prednisolone to control an RR after the initial period." In other words, initial tapering from 40 to around 20 mg would not lead to deterioration, but then subsequent attempts to dip below the 15-20 mg level would often necessitate having to go back to the previous higher dose to counteract the flare-up. The outcome of this strategy of controlled tapering under careful monitoring of nerve function for sometimes very long periods of time (up to 20 months for borderline lepromatous patients) was compared to the outcome of the more rigid standardized 2-3 month treatment strategies used earlier and it was found that the results were far superior.

Little *et al.* [19] demonstrated in cytokine profile studies of patients with RR that prednisolone only starts to have an effect 28 days after starting treatment and that treatment may be needed for up to six months because some patients continued to have cytokine production for one to six months.

As mentioned earlier, no RCT was found that could provide hard evidence for the efficacy of prednisolone in ENL or type II reaction. However, non-randomized evidence

[20-22] questions the use of prednisolone for ENL in the fixed regimens advised by WHO at the very least. ENL treatment is found to be much less straightforward than RR because it tends to be episodic with many patients suffering from chronic or recurrent ENL. Most ENL patients require pulse therapy with very high doses of prednisolone given for a short period of a few days to one week after which it can be tapered rapidly within two to three weeks to avoid steroid dependence and side effects [4]. Most ENL episodes last < 1 month and therefore do not require the 12-week prednisolone regimen advocated by WHO. Moreover, the starting dose of prednisolone in this regimen is too low for most cases of severe ENL.

Pannikar [23] states that there is no role for thalidomide in (chronic) ENL because of its teratogenicity and because "today ENL reaction is a rare complication, limited to a small proportion of MB patients".

Alternative treatments such as surgical decompression of inflamed nerves do exist but are not considered here because they are not feasible as standardized treatment regimens in field conditions.

**DISCUSSION**

**Main Results**

Only three RCT's analyzed in one Cochrane review were found as randomized evidence and none of them found a significant difference in nerve function improvement in the intervention group compared to placebo after one year of follow-up. However, the results do indicate that the duration and dosages used in the intervention groups may have been insufficient. This is backed up by most of the non-randomized evidence.

The findings by Van Brakel & Khawas [14], Becx-Bleumink *et al.* [15], Britton [16] and Saunderson *et al.* [17]

seem to back up the results of the RCT (Van Brakel *et al.* 2003) with the group of patients with mild sensory impairments. More importantly, the favorable results found at the end of the four month treatment period becoming insignificant at the 6-month follow-up point suggest that even the 16 week regimen is too short to achieve good long-term results. The Ethiopian study by Saunderson *et al.* [17] found that it may take a much longer time than the duration of a standard steroid course “to achieve full recovery of chronic or recurrent nerve function impairment.” The RCT [12] with the long standing nerve function impairment group revealed spontaneous improvement amongst 49% of the placebo group after 12 months, as opposed to 46% of those treated with prednisolone. This is in line with the 51% found in the Ethiopian study, suggesting that doing nothing for this group is as good as treating with steroids. However, the duration of treatment in the RCT (16 weeks) may be highly insufficient for this group, even more so than for the group with mild sensory impairments.

When analyzing the retrospective study by Naafs *et al.* [18], it would appear that the individually tailored anti-reaction treatment strategy he used cannot be feasible in field conditions, where fixed schedules would need to be recommended and implemented for operational reasons. The crucial point, however, is the length of time the prednisolone dose stays above the 15-20mg level. If this period is sufficiently long, even in standardized fixed-dose regimens needed in the field, the long-term outcome seems to be favorable. In fact, the earlier field regimens [24], which were much longer than the one advised by WHO, generally showed good results, although long-term follow-up was not done at the time.

The RCT [11] comparing three steroid regimens, included in the review mentioned above, supports the findings by Naafs *et al.* [18] and Little *et al.* [19]. The longer (5 month) regimens - both low and high-dosed - resulted in significantly less patients needing additional corticosteroids during a twelve month period than the shorter (3 month) regimen. The need for extra corticosteroids - determined by the “failure to respond to treatment in terms of changes to skin lesions, nerve pain or tenderness, or nerve function, or recurrences of skin or nerve lesions...” - was defined as a poor outcome in this trial.

Pannikar’s claims about the role of thalidomide are not backed up by references to evidence [23]. Being a spokesperson for WHO, his views are reflected in the WHO guidelines for the treatment of ENL, where prednisolone is the drug of choice for single episodes of ENL and clofazimine or a combination of clofazimine and (lower-dosed) prednisolone is the drug of choice for recurring or chronic ENL. Some experts, however, beg to differ. Pereira presents data from Brazil showing that 50% of all patients diagnosed with leprosy are MB and that 30% of these develop ENL [25]. If 15 out of every 100 patients who are diagnosed with leprosy develop ENL, the condition cannot be considered rare or “limited to a small proportion of MB patients”. The teratogenicity of thalidomide is not disputed by any expert but the drug is found to be extremely effective for especially chronic ENL requiring maintenance therapy, far more effective than the clofazimine maintenance therapy advocated by WHO.

## Limitations

When searching for evidence in favor or against current treatment guidelines, a lot of emphasis was put on finding RCT’s that comply with very rigid criteria. It could be argued that there may be a lot of very valid “circumstantial evidence” that does not filter through because of these criteria and is thus lost.

Since only a few randomized controlled trials have been conducted in this field, we did our best to take the other evidence we did find with our search strategy into account, reviewing it in light of the findings of the review trials. Most of this non-randomized evidence clearly does not support the treatment guidelines, but it may be that evidence that does support the guidelines - thus may have been a decisive factor for the implementation of the existing guidelines by the authorities responsible - was lost due to our search method.

## Impact

As mentioned earlier in this document, approximately 5 million new leprosy patients are expected globally in the coming 20 years with the current elimination campaign. About 30% of these can be expected to develop a reaction sooner or later during the course of their disease, although these percentages can fluctuate depending on the quality of the leprosy control services. The better the services, the earlier the detection and thus the less chance of developing a reaction. Assuming an optimistic view that leprosy services in general will be maintained and improved, thus guaranteeing earlier detection than is the case now, the percentage of 30% of 5 million ( $\approx 1.500.000$ ) developing reactions might be halved to 15% ( $\approx 750.000$ ) with 50% ( $\approx 375.000$ ) of those developing RR of less than 6 months duration. We saw in the Van Brakel trial that 75% of these patients recover spontaneously. This would imply that with current WHO guidelines, 25% of 375.000, thus 93.750 patients (or about 4700 patients per year), would be given insufficient treatment. It is clear from this review it is time for a change, especially when taking into account that the calculations above are those of a best case scenario.

## Future Research: Recommendation for an RCT Dealing with RR

Ideally, a randomized trial should be large enough to yield both conclusive results and detect adverse events with some degree of precision. The RCT’s dealing with RR described above point toward a need for longer trials with higher doses of prednisolone while at the same time none of them report more serious adverse effects for the steroid groups, even in the higher-dosed 5-month trial. Data from the prolonged treatment groups in the (non-randomized) Naafs *et al.* [18] study also do not show a significant increase in the number of serious side effects. A priori, therefore, none of the data suggest that a longer trial with higher prednisolone doses might be ethically contra-indicated. However, an individual RCT is rarely large enough to detect (rare) adverse effects by itself. Combining the data from other individual trials in a systematic review might then provide high enough numbers of patients to detect these rare side effects.

**Table 4. Dosage and Tapering Schedule for a Two-Armed RCT for Field Treatment of RR**

1 <sup>st</sup> Arm (slow tapering)		2 <sup>nd</sup> Arm (fast tapering)	
Period	Daily Dose (not exceeding 1 mg per kg body weight)	Period	Daily Dose (not exceeding 1 mg per kg body weight)
Week 1 and 2	40 mg	Week 1 and 2	40 mg
Week 3 and 4	40 mg	Week 3 and 4	35 mg
Week 5 and 6	35 mg	Week 5 and 6	30 mg
Week 7 and 8	35 mg	Week 7 and 8	25 mg
Week 9 and 10	30 mg	Week 9 and 10	20 mg
Week 11 and 12	30 mg	Week 11 and 12	20 mg
Week 13 and 14	25 mg	Week 13 and 14	20 mg
Week 15 and 16	25 mg	Week 15 and 16	20 mg
Week 17 - 20	20 mg	Week 17 - 20	20 mg
Week 21 and 22	15 mg	Week 21 and 22	15 mg
Week 23 and 24	10 mg	Week 23 and 24	10 mg
Week 25 and 26	5 mg	Week 25 and 26	5 mg
Total 26 weeks	STOP	Total 26 weeks	STOP
Total dose	4620 mg		3920 mg

A starting dose of 40 mg for RR (in contrast to ENL, where non-randomized evidence suggests much higher starting doses are required) seems acceptable to most authorities. Taking the existing evidence into account, a double blind randomized trial could be set up comparing two strategies of equal length, both maintaining prednisolone levels of 20 mg or above for 20 weeks (~5 months), but one arm tapering from 40 to 20 mg at a slower rate than the other. A comparison of a longer strategy with one of the strategies followed in the RCT’s in the review would be considered unethical because there was no significant difference found after one year follow-up when compared with placebo; a comparison with the WHO strategy even more so because it is considerably shorter than any of the RCT trials in the Cochrane review. Table 4 summarizes a suggested course of action.

This strategy would maintain prednisolone levels equal to or above 15mg for 22 weeks, significantly longer than the 8 weeks in the WHO strategy and longer than the 12 weeks in the RCT’s which already yielded beneficial (albeit temporary) results. It might be argued that the period of 26 weeks is unacceptably long for field treatment because of adherence and loss-to-follow-up issues, but Sundar Rao [11] did not find significant differences in “treatment not completed” rates in the 5-month groups compared to the 3-month group, while 5 months is only slightly shorter than the 26 weeks suggested here, and his groups were also treated in an ambulatory way with blister packs.

A number of criteria would have to be met. Besides the criteria necessary to validate the trial as a sound RCT, the follow-up of the participating patients should be sufficiently long (perhaps two years) and complete for the outcome to occur. Crucially, the outcome to be measured should not only be the need for extra corticosteroids during the follow-

up period, but also sensory and voluntary muscle testing scores at fixed points in time as well as the occurrence of major adverse effects.

**CONCLUSIONS**

Evidence from RCT’s suggest that the current WHO strategy of treating RR for 12 weeks in field conditions is not efficacious in the long run. The intervention does not yield significantly better outcomes than a placebo group. Evidence from RCT’s and further non-randomized evidence suggest that higher doses of prednisolone (15-20mg) need to be maintained for much longer periods (perhaps up to 6 months) than is now the practice. More trials are needed (with sufficiently long follow-up) to determine the optimal doses and length of treatment.

Non-randomized evidence suggests that the 12-week prednisolone regimen may not be suitable for ENL. Field treatment may not be feasible because of the episodic and recurring nature of ENL. Furthermore, the role of thalidomide needs to be reassessed. RCT’s need to be initiated comparing the current strategy with alternatives.

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