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Van Veen, NH; Lockwood, DN; Van Brakel, WH; Ramirez, JJr;
Richardus, JH (2009) Interventions for erythema nodosum leprosum.
A Cochrane review. *Leprosy review*, 80 (4). pp. 355-72. ISSN 0305-
7518

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REVIEW

Interventions for erythema nodosum leprosum. A Cochrane review

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Accepted for publication 09 September 2009

Summary

Introduction Treatment for erythema nodosum leprosum (ENL), an immunological complication of leprosy, is diverse. We undertook a systematic review as it was not clear which treatments were most beneficial.

Methods We did a systematic search to identify randomised controlled trials (RCTs) comparing treatment with placebo, no treatment or another therapy. Two authors assessed quality and checked data.

Results We included 13 studies involving 445 participants. These trials assessed: betamethasone, thalidomide, pentoxifylline, clofazimine, indomethacin and levamisole. The quality of the trials was generally poor and no results could be pooled due to the treatments being so heterogeneous. Treatment with thalidomide showed a significant benefit compared to aspirin (RR 2.43; 95% CI 1.28 to 4.59). Clofazimine treatment was superior to prednisolone (more treatment successes; RR 3.67; 95% CI 1.36 to 9.91) and thalidomide (fewer recurrences; RR 0.08; 95% CI 0.01, 0.56). Minor adverse events were significantly lower in participants on a low dose thalidomide regimen compared to a high dose thalidomide regimen (RR 0.46; 95% CI 0.23 to 0.93). Significantly more minor adverse events were reported in participants taking clofazimine compared with prednisolone (RR 1.92; 95% CI 1.10 to 3.35). None of the studies assessed quality of life or economic outcomes.

Conclusion There is some evidence of benefit for thalidomide and clofazimine, but generally we did not find clear benefits for interventions in the management of ENL.

This does not mean they do not work because the studies were small and poorly reported. Larger studies using clear definitions and internationally recognised scales are urgently required.

Introduction

This paper is based on a Cochrane review first published in The Cochrane Library 2009, Issue 3 (see <http://www.thecochranelibrary.com/> for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.

Erythema nodosum leprosum (ENL) or Type 2 leprosy reaction is an immune-mediated complication of leprosy, causing inflammation of skin, nerves and other organs, and general malaise.^{1–3} ENL only occurs in people with borderline lepromatous (BL) and lepromatous (LL) leprosy. These people have high bacterial loads which increase the risk of ENL. The reported prevalence of ENL among these people is highly variable with high rates (up to 50%) in Asia⁴ and lower rates (up to 12%) in Africa.⁵ Most people with ENL have multiple acute episodes of ENL or chronic ENL over several years. Few people experience a single acute episode of ENL.⁴

Therapies for ENL aim to control the acute inflammation, relieving the pain and preventing further nerve damage or new episodes. The conventional treatment for mild ENL is rest and anti-inflammatory medication. Aspirin is the most commonly used anti-inflammatory drug, but indomethacin, chloroquine and colchicine have been tested as well.^{2,6} For severe ENL, prednisolone and clofazimine are most commonly used. Prednisolone usually acts rapidly by controlling the acute inflammation and relieving the pain. The starting dose should be the lowest possible to control ENL and be gradually reduced. The schedule for reducing prednisolone depends on the course of the disease. ENL is often recurrent or chronic and requires high-dose and prolonged courses of prednisolone for the disease to be controlled. This increases the risk of adverse events, such as hypertension or diabetes, and steroid dependency.^{2,6} Clofazimine is considered a useful anti-inflammatory drug when corticosteroids are contraindicated or need to be reduced. However, treatment with clofazimine usually takes 4 to 6 weeks to become active and the dose of clofazimine needed to control ENL is higher than the dose used in multi drug therapy (MDT). Disadvantages of continuous high doses of clofazimine are gastrointestinal symptoms (e.g. diarrhoea) and dark discoloration of the skin.^{2,6,7} Another drug used to treat ENL is thalidomide. The effectiveness of thalidomide in ENL is primarily due to its action on the proinflammatory cytokine TNF but other mechanisms may contribute to its anti-inflammatory effect.⁸ The seventh WHO Expert Committee on Leprosy considered thalidomide as an effective treatment of severe ENL, and recommended to restrict thalidomide treatment to male or post-menopausal female patients only. Thalidomide should only be given to women of childbearing age when comprehensive contraceptive precautions can be taken, because its use may cause serious birth defects when taken in early pregnancy.⁹

ENL is a serious immunological complication of leprosy. The complex mechanisms underlying ENL are not fully understood yet, which makes treatment difficult. Corticosteroids, clofazimine and thalidomide are the drugs of choice for ENL, but all have drawbacks and the optimal regimen has not been established. Alternative therapies (e.g. ciclosporin, oral zinc) have been tested, but it is unclear if they are beneficial, or which one is preferable. The role of newer treatments, such as TNF- α antibody treatment, intravenous immunoglobulin, and tenidap, is not known.

Methods

SEARCH STRATEGY

We searched the Cochrane Skin Group Specialised Register using the following search terms: (leprosy and Type and 2) or lepromatous or lepra* or (erythema and nodosum) or 'ENL' or (leprosy and borderline) or leprosum. This search strategy, combined with a search strategy for identifying randomised trials, was adapted to include additional search terms where necessary and was modified to search the Cochrane Central Register of Controlled Trials (*Cochrane Library*, Issue 1, 2009), MEDLINE (from 2003), EMBASE (from 2005), LILACS and AMED (from inception), CINAHL (from 1981) and databases of ongoing trials. All searches were done in March 2009. We checked reference lists of articles. We contacted a person to locate studies from Brazil. There were no language restrictions. Two authors checked the titles and abstracts of all the publications identified to examine which studies were eligible.

STUDY SELECTION

Studies were eligible if they were randomised controlled trials (RCTs) assessing any therapy for ENL, including systemic corticosteroids, systemic non-steroidal immunomodulatory therapies and diverse therapies. We used the following definition of ENL: 'an inflammatory condition, in which people develop crops of tender erythematous subcutaneous skin lesions'. There may be accompanying neuritis, iritis (inflammation of the iris), arthritis, orchitis (inflammation of the testis), dactylitis (inflammation of the fingers and toes), lymphadenopathy, oedema and fever. The skin signs are obligatory; the nerve and general signs optional.^{10,11} The primary outcome measure of interest was the proportion of participants achieving remission of skin lesions. Remission was defined as the absence of new tender erythematous subcutaneous skin lesions at completion of the ENL therapy, as assessed by a clinician. Secondary outcome measures were: the proportion of participants achieving remission of inflammations at other sites, investigator-assessed change in ENL severity, time to next clinical episode of ENL and changes in quality of life. We considered data that had been recorded for 4 weeks or less from the start of treatment to reflect short-term benefit and these were analysed separately from data that were recorded for more than 4 weeks from the start of treatment, which we considered to reflect the minimum time period to capture any longer-term benefit. The short-term assessment (1 to 4 weeks) was considered the primary endpoint, because the definite treatment effects should be visible within the first few weeks. The medium-term assessment (between 4 weeks and 6 months) was used as a secondary endpoint. Assessments of more than 6 months after the start of treatment were considered long-term outcomes.

METHODOLOGICAL QUALITY

The methodological quality of the included studies was based on the following criteria: the method of generation of the randomisation sequence; the method of allocation concealment; who was blinded/not blinded (participants, clinicians, outcome assessors); how many participants were lost to follow-up in each arm and whether participants were analysed in the groups to which they were originally randomised (intention to treat principle); degree of certainty that participants had ENL; baseline comparison for age, sex, duration and severity of ENL; whether outcome measures were clearly described.

Each criterion was assessed as A: adequate, B: unclear or C: inadequate. If one of the criteria was not described in the study, it was labelled 'inadequate'. Two authors independently assessed the included studies for methodological quality.

DATA EXTRACTION AND ANALYSIS

One author extracted data regarding methodology and outcome measures from the included studies onto a data extraction form, and a second author checked the data. If there were missing data, the trial authors were contacted. Authors were not blinded to trial author, journal or institution. We used the Cochrane statistical package, Review Manager, for statistical data analysis. Results were expressed as mean differences with 95% confidence intervals (CI) for continuous outcome measures and relative risks (RR) with 95% CI for dichotomous outcomes. We were not able to pool results from studies due to treatments and outcomes being so heterogeneous, and did not perform sensitivity analysis. We did not perform further subgroup analysis due to lack of data on different subgroups (mild versus severe ENL; single acute versus multiple acute versus chronic ENL). Adverse effects that were reported in the included studies were described.

Results

STUDY SELECTION

We found 269 citations to potentially relevant trials from the electronic searches. Eight potentially eligible studies were found from references of included trials and reviews. Correspondence with authors and other people, and searching of grey literature revealed one potentially relevant trial. We identified 48 possible studies, of which 13 were RCTs. The search of the ongoing trial registers revealed one ongoing trial. We excluded 35 studies of which 21 were not RCTs, two were excluded as they did randomisation by alternation, 10 did not have ENL as inclusion criterion, but included participants with lepromatous leprosy in general, one was a duplicate study and one was excluded because it described only intake results and was not completed.

CHARACTERISTICS OF INCLUDED STUDIES

We included 13 trials with 445 participants in this review and characteristics of these studies are shown in Table 1.

Ten studies were published between 1969 and 1985 and three studies between 2002 and 2007. Three trials had a cross-over design and 10 trials had a parallel group design, of which one trial had four parallel groups. The studies involved sample sizes between nine and 92 participants. Two studies randomised and evaluated ENL reactions of participants. The age range of participants in eight studies was 14 to 69 years, five studies did not report information on the age of the participants. Five studies included both males and females, four studies included only males, and four studies did not report this information. The duration of ENL reactions varied from 0–12.5 years in eight trials, and five trials did not report this information. The severity of reactions ranged from mild to severe and was reported in eight trials.

Table 1. Characteristics of included studies

Study	Method	Participants	Interventions	Outcomes
Girdhar 2002	Parallel group design	Setting: single centre, leprosy centre, India Incl: lepromatous leprosy wit recurrent ENL and on steroids for > 6 months, excl: not stated M/F: not stated, age: not stated, duration: not stated, severity: not stated Randomised: 10 participants Evaluable: 9 participants (1 lost to follow-up)	Experimental group (<i>n</i> = 4): infusion of betamethasone in 5% dextrose daily for 3 days every 4 weeks for 6 months Control group (<i>n</i> = 5): infusion of 5% dextrose daily for 3 days every 4 weeks for 6 months Other therapy: MDT with 100 mg clofazimine daily for all participants; oral steroids as per need to control ENL for participants in control group	1) Change in severity and frequency of ENL 6 months after end of treatment 2) Steroid requirement 3) Side effects
Pearson 1969	Cross over design	Setting: single centre, leprosy centre, Malaysia Incl: moderately severe ENL, Excl: not stated M/F: 11/1, age: not stated, duration: 10 months to 3-5 years, severity: unclear, though title states was moderately severe ENL Randomised: 12 participants Evaluable: 12 participants (1 from group B withdrawn from study after 9 weeks)	Group A (<i>n</i> = not stated): thalidomide tablets (100 mg 3 times daily) for 6 weeks, followed by placebo (dose and frequency unknown) for 6 weeks Group B (<i>n</i> = not stated): placebo tablets (dose and frequency not stated) for 6 weeks, followed by thalidomide tablets (100 mg 3 times daily) for 6 weeks Other therapy: prednisolone, stibophen and paracetamol in addition to placebo	1) Change in ENL score 2) Steroid requirement 3) Side effects
Waters 1971	Cross over design	Setting: single centre, leprosy centre, Malaysia Incl: not stated, but included were participants with lepromatous leprosy and histologically confirmed moderately severe or severe chronic ENL, excl: not stated M/F: 10 M, age: 19–56, duration: 9 months to 3-5 years, severity: moderately severe or severe chronic ENL Randomised and evaluable: 9 participants (16-week trial), 8 participants (24-week trial)	16-week trial (<i>n</i> = 9) and 24-week trial (<i>n</i> = 8): Group A (<i>n</i> = 5 or <i>n</i> = 3): thalidomide tablets (100 mg 3 times daily) for 4 or 6 weeks, followed by placebo tablets (dose unknown, 3 times daily) for 4 or 6 weeks Group B (<i>n</i> = 4 or <i>n</i> = 5): placebo tablets (dose unknown, 3 times daily) for 4 or 6 weeks, followed by thalidomide tablets (100 mg 3 times daily) for 4 or 6 weeks Other therapy: 100 mg DDS twice weekly, prednisolone or corticotrophin daily, mild analgesics if needed	1) Steroid requirement during trial period 2) ENL score (temperature, severity)

Table 1. continued

Study	Method	Participants	Interventions	Outcomes
Sheskin 1969	Parallel group design	Setting: single centre, hospital/ambulatory, Venezuela Incl: lepromatous leprosy with clearly demonstrable dermatologic, neurologic or other manifestations of ENL reaction, excl: not stated M/F: 37/15, age: 17–58, duration: 3 months to 9 years, severity: not stated Randomised and evaluable: 173 ENL reactions (of 52 participants)	Experimental group ($n = 85$): thalidomide tablets (100 mg 4 times daily if > 50 kg, or 6 mg/kg/day if ≤ 50 kg) for 7 days Control group ($n = 88$): placebo tablets (100 mg 4 times daily if > 50 kg, or 6 mg/kg/day if ≤ 50 kg) for 7 days Other therapy: if on sulfone therapy at admission, sulfone therapy was continued; if receiving steroids or ACTH for prolonged periods at admission, same dosage was continued	1) Total improvement, defined as all dermatologic manifestations in advanced state of remission, no new elements, disappearance of characteristic lepra reaction symptoms after 7 days 2) Side effects
Iyer 1971	Parallel group design	Setting: multicentre, 4 centres, India, Mali, Somalia, Spain Incl: clearly demonstrable dermatological signs of acute lepra reactions, excl: severe or life-threatening lepra reactions M/F: 92 M, age: 15–55 +, duration: not stated, severity: not stated Randomised and evaluable: 214 ENL reactions (of 92 participants)	Experimental group ($n = 116$): thalidomide tablets (100 mg 4 times daily if ≥ 50 kg, or 100 mg 1–3 times daily if < 50 kg) for 7 days Control group ($n = 98$): acetylsalicylic acid tablets (400 mg 4 times daily if ≥ 50 kg, or 400 mg 1–3 times daily if < 50 kg) for 7 days Other therapy: upon admission all drug therapy had to be ceased	1) No further reactions 2) Changes in temperature, skin lesions, blood pressure, pulse rate and blood cell count after 7 days 3) Side effects
Villahermosa 2005	Parallel group design	Setting: single centre, leprosy centre, Philippines Incl: lepromatous leprosy, ≥ 18 years, acute histologically confirmed episode of ENL consisting of ≥ 10 skin nodules, with or without systemic symptoms; women only included if evidence of non-childbearing potential, excl: incapacitating ENL (bed ridden), severe neuritis, thalidomide ingestion within 30 days or corticosteroid ingestion within 2 weeks of enrolment M/F: 22 M, age: 18–46, duration: 0–3 years, severity: not stated Randomised: 22 participants Evaluable: 19 (3 lost to follow-up)	Group A ($n = 12$): thalidomide capsules, 100 mg daily (2 \times 50 mg, 4 \times dummy capsules) in week 1, 50 mg daily (1 \times 50 mg, 3 \times dummy capsules) in week 2–3, 4 \times dummy capsules daily in week 4–7 Group B ($n = 10$): thalidomide capsules, 300 mg daily (6 \times 50 mg, 0 \times dummy capsules) in week 1, 200 mg daily (4 \times 50 mg, 0 \times dummy capsules) in week 2–3, 100 mg daily (2 \times 50 mg, 2 \times dummy capsules) in week 4–5, 50 mg daily (1 \times 50 mg, 3 \times dummy capsules) in week 6–7 Other therapy: acetaminophen for participants with fever during first 72 h of study	1) Resolution of inflamed ENL nodules during initial 7-day treatment 2) Global assessment 3) Re-emergence of skin lesions during taper 4) Week 7 lesion counts 5) Recurrence of lesions after taper 6) Safety and adverse events

Table 1. *continued*

Study	Method	Participants	Interventions	Outcomes
Sales 2007	Parallel group design	Setting: single centre, leprosy centre, Brasil Incl: MB leprosy, males between 18–60 y, females over 49 (postmenopausal), clinical and histopathological ENL, excl: acute neuritis requiring CS, hepatic, renal, mental diseases, diabetes and/or immune-deficiencies related to HIV M/F: 38/6, age: 18–69, duration: not stated, severity: not stated Randomised: 44 participants Evaluable: 44 participants (8 lost to follow-up)	Group A (<i>n</i> = 24): pentoxifylline (1.2 g daily) for 30 days Group B (<i>n</i> = 20): thalidomide (300 mg daily) for 30 days Other therapy: participants with no improvement after 15 days treatment or with severe adverse effects were removed from study and put on recommended regimen of thalidomide or corticosteroids	1) Improvement at end of 30 days treatment, defined as complete elimination of type 2 reactional skin lesion inflammation, normal body temperature and/or regression of systemic symptoms 2) Side effects
Helmy 1971	Cross over design	Setting: single centre, leprosy centre, Malaysia Incl: not stated, though included were lepromatous or indefinite leprosy with moderately severe ENL, excl: not stated M/F: 10/5, age: 17–67, duration: 6 months to 2 years, severity: moderately severe ENL Randomised: 15 participants Evaluable: 10 participants (5 lost to follow-up)	Group A (<i>n</i> = 3): clofazimine capsules (100 mg 3 times daily) in week 1–4, followed by placebo capsules (dose unknown, 3 times daily) in week 5–8 Group B (<i>n</i> = 7): placebo capsules (100 mg 3 times daily) in week 1–4, followed by clofazimine capsules (dose unknown, 3 times daily) in week 5–8 Other therapy: dapsone (100 mg 2 times daily); stibophen if needed; paracetamol issued twice weekly to be taken freely	1) Severity score of ENL

Table 1. *continued*

Study	Method	Participants	Interventions	Outcomes
Iyer 1976	Parallel group design	Setting: single centre, India Incl: male, lepromatous leprosy and prone to recurrent reactive episodes, excl: not stated M/F: 72 M, age: 15–54, duration: <6 months to > 4 years, severity: moderate, severe Randomised: unclear, states '72 participants available for analysis' Evaluable: 72 participants	Experimental group ($n = 36$): clofazimine (100 mg 3 times daily) for 8 weeks, clofazimine (100 mg once a day) + dapsone (10 mg/kg/week) for 52 weeks Control group ($n = 36$): thalidomide (100 mg 3 times daily) for 8 weeks, thalidomide (25–50 mg once a day) + dapsone (10 mg/kg/week) for 52 weeks Other therapy: dapsone (10 mg/kg/week) for 52 weeks	1) Time to control reaction 2) Maintenance of anti-reaction effect after therapy
Karat 1970	Parallel group design	Setting: single centre, leprosy centre, India Incl: history of ≥ 3 severe reactions and with severe current reaction which could not be controlled by antimony, aspirin or chloroquine, excl: peptic ulcer, intercurrent acute infections, TB or malignant lesions M/F: not stated, age: not stated, duration: 4–150 months, severity: severe Randomised and evaluable: 24 participants	Experimental group ($n = 12$): clofazimine (100 mg 3 times daily) for 12 weeks Control group ($n = 12$): prednisolone (10 mg 3 times daily) week 1, (10 mg 2 times daily) week 2, (5 mg 3 times daily) week 3, (10 mg 2 times daily) week 4, (5 mg once daily) week 5–12 Other therapy: none	1) Treatment success at end of 12 weeks, defined as body temp < 37.2°C, no new ENL lesions, no pain in peripheral nerve, no progression of neurological deficit, and iritis quiescent in 2 weeks from starting treatment 2) Recurrence of reaction during trial 3) Side effects
Ing 1969	Parallel group design	Setting: single centre, Singapore Incl: Lepromatous leprosy and ENL (mild, moderate or severe), excl: not stated M/F: not stated, age: not stated, duration: not stated, severity: 15 mild, 9 moderate, 6 severe Randomised: 30 participants Evaluable: 30 participants, though one participants did not complete 4-week treatment	Experimental group ($n = 16$): indomethacin (25 mg 3 times daily) for 1 month Control group ($n = 14$): prednisolone (5 mg 3 times daily) for 1 month Other therapy: anti-leprosy drugs were given during 4-week trial period, but no additional analgesics	1) Improvement after 4 weeks (e.g. mean change in pain relief, subsidence of lesions) 2) Side effects

Table 1. *continued*

Study	Method	Participants	Interventions	Outcomes
Karat 1969	Parallel group design	Setting: single centre, leprosy centre, India Incl: lepromatous leprosy with ENL, > 12 years, excl: history or radiological evidence of peptic ulcer, diabetes, TB, hypertension, severe intercurrent infection, acute peripheral nerve paralysis, medical conditions requiring use of other anti-leprosy drugs M/F: not stated, age: not stated, duration: not stated, severity: 28 mild, 22 severe Randomised and evaluable: 50 participants	Group 1 (<i>n</i> = 11): indomethacin orally (50 mg 3 times daily) in wk 1–2, (25 mg 3 times daily) in week 3, (25 mg once a day) maintenance Group 2 (<i>n</i> = 12): chloroquine orally (250 mg 3 times daily) in wk 1–2, (250 mg 2 times daily) in week 3, (250 mg once a day) maintenance Group 3 (<i>n</i> = 13): prednisolone orally (5 mg 3 times daily) in wk 1–2, (5 mg 2 times daily) in week 3, (5 mg once a day) maintenance Group 4 (<i>n</i> = 14): aspirin orally (1 g 3 times daily) in wk 1–2, (1 g 2 times daily) in week 3, (500 mg 2 times daily) maintenance Other therapy: anti-leprosy drugs were stopped on admission; sedation with phenobarbitone or chlorpromazine if needed; diuretics only when oedema was progressive and uncontrolled by one of the given drugs	1) Control of reaction 2) Recurrence of reaction 3) Side effects
Arora 1985	Parallel group design	Setting: single centre, hospital, India Incl: 12 participants with ENL, excl: not stated M/F: 11/1, age: 14–55, duration: 0–7 years, severity: severe Persons analysed: 269 (a: 88, b: 91, c: 90) Randomised and evaluable: 12 participants	Experimental group (<i>n</i> = 5): levamisole capsules (150 mg daily) on 3 consecutive days repeating every fortnight for 3 months Control group (<i>n</i> = 7): placebo capsules (dose unknown, daily) on 3 consecutive days repeating every fortnight for 3 months Other therapy: iron for anaemic participants	1) Improvement, defined as complete recovery from reaction, after 3 months

INTERVENTIONS

The included studies examined the following interventions.

Systemic corticosteroids:

- infusion of betamethasone in 5% dextrose versus infusion of 5% dextrose¹²

Systemic non-steroidal immunomodulatory therapies:

- thalidomide versus placebo^{13–15}
- thalidomide versus acetylsalicylic acid¹⁶
- 100 mg thalidomide regimen versus 300 mg thalidomide regimen¹⁷
- pentoxifylline versus thalidomide¹⁸
- clofazimine versus placebo¹⁹
- clofazimine versus thalidomide²⁰
- clofazimine versus prednisolone²¹
- indomethacin versus prednisolone²²
- indomethacin versus chloroquine versus prednisolone versus aspirin²³
- levamisole versus placebo²⁴

Diverse therapies:

- none

OUTCOME MEASURES

The outcomes remission of skin lesions and remission of inflammation at other sites were not explicitly reported in any of the trials. Seven trials used different grading scales or scores to assess ENL severity. The secondary outcome of time to next clinical episode was not reported in any of the trials. None of the studies measured changes in quality of life or economic outcomes. Adverse effects were not reported in three trials.

Six trials recorded data only for 4 weeks or less from the start of treatment, reflecting short-term benefit. Three trials had the outcome assessment at medium term, ranging from 4 weeks to 6 months from the start of treatment. One trial assessed long-term benefit, more than six months after treatment. One trial assessed both on short-term and medium-term, and one trial both on medium-term and long-term. The timing of outcome assessment was unclear in one trial.

METHODOLOGICAL QUALITY

The methodological quality of the trials was generally poor. The results of the assessment of methodological quality are shown in Table 2.

None of the trials was clear as to how randomisation lists were generated. Concealment of allocation was considered adequate in two trials which had the medication pre-prepared by a drug company.^{16,17}

Table 2. Assessment of methodological quality

Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias*
Girdhar 2002	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
Pearson 1969	Unclear	Unclear	Unclear	Yes	No	Unclear
Waters 1971	Unclear	Unclear	Unclear	Unclear	No	Unclear
Sheskin 1969	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
Iyer 1971	Unclear	Yes	Unclear	Unclear	Unclear	Unclear
Villahermosa 2005	Unclear	Yes	Unclear	No	Yes	Unclear
Sales 2007	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Helmy 1971	Unclear	Unclear	Unclear	No	Unclear	Unclear
Iyer 1976	Unclear	Unclear	No	Unclear	Unclear	Unclear
Karat 1970	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Ing 1969	Unclear	Unclear	Unclear	Unclear	No	Unclear
Karat 1969	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
Arora 1985	Unclear	Unclear	Unclear	Unclear	Yes	Unclear

* Certainty of diagnosis, baseline comparison, explicit outcomes.

Blinding of outcome assessment was attempted for most of the trials, but none of the studies clearly described who (the participants, clinicians and outcome assessors) was blinded.

Information about incomplete outcome data was generally not reported and participant losses ranged between 0 and 33%. Seven trials did not report information on incomplete outcome data, but if accepting no mention in the text and no signs of attrition in tables, as a 100% follow-up, all of these trials had a follow-up rate of 100%. Six trials reported missing data and two performed intention to treat analysis.

Six trials did not perform a statistical analysis, but only described the results. One study²² reported in the summary that 'indomethacin is effective in treating only mild and moderate cases of ENL'. The summary of one study¹⁴ concluded that 'nine of the 10 participants showed a very significant improvement'. Another study¹³ summarised that 'thalidomide was superior to a placebo'. None of these studies provided sufficient evidence (e.g. significant test values) to support these claims.

Five studies specified erythema nodosum leprosum (ENL) in their inclusion criteria. Most other studies did not define ENL, but did mention it under the inclusion criteria. Five studies did not provide data for baseline comparison and seven studies were not clear as to whether groups were similar at baseline. Six studies did not clearly describe outcome measures.

EFFECTS OF INTERVENTIONS

Subgroup analysis was not performed as there were no appropriate studies to pool. Of the 13 studies included, none compared the same interventions or had comparable outcomes. We did not find any trials assessing diverse therapies for ENL. Quality of life and economic outcomes were not included in any of the trials.

Primary Outcome Measure

(A) THE PROPORTION OF PARTICIPANTS ACHIEVING REMISSION OF SKIN LESIONS

None of the studies reported the absence of new skin lesions at the end of therapy. Two studies had outcome measures that were considered to reflect our primary outcome measure, Karat *et al.*²¹ reported treatment success, including absence of new ENL lesions and Sheskin *et al.*¹⁵ reported improvement, including absence of new ENL lesions, but did not provide separate data of the first randomised treatment regimen for comparison. Five studies reporting differing definitions of remission of skin lesions. One study reported the number of participants with no further reaction after the first treatment regimen, implying absence of new ENL skin lesions.¹⁶ Three studies reported the resolution of existing skin lesions.^{17,18,22}

Systemic corticosteroids

Remission of skin lesions was not reported for any systemic corticosteroid interventions.

Systemic non-steroidal immunomodulatory therapies

Short-term: Significantly more participants who received thalidomide treatment had no further reaction after 7 days, requiring a second treatment regimen, compared to those

receiving acetylsalicylic acid (aspirin) treatment (RR 2.43; 95% CI 1.28 to 4.59; $n = 92$).¹⁶ No significant difference in resolution of existing inflamed ENL nodules was found between the 100 mg thalidomide regimen and the 300 mg thalidomide regimen after 7 days (RR 1.33; 95% CI 0.64 to 2.79; $n = 22$).¹⁷ No significant difference in the resolution of existing inflamed ENL skin nodules was observed between pentoxifylline and thalidomide after 30 days of treatment (RR 1.05; 95% CI 0.74 to 1.49; $n = 25$).¹⁸ No significant difference in complete subsidence of existing ENL lesions was found between indomethacin and prednisolone after 4 weeks (RR 2.33; 95% CI 0.76 to 7.13; $n = 30$).²²

Medium-term: One participant, who had received the 300 mg thalidomide regimen, had a successful taper, defined as a complete response after 7 days and lack of new acutely inflamed lesions during the 6 week taper and for at least 2 months after stopping thalidomide.¹⁷ Significant more treatment successes were observed in the clofazimine group compared to the prednisolone group at the end of 12 weeks of treatment (RR 3.67; 95% CI 1.36 to 9.91; $n = 24$).²¹

Secondary Outcome Measures

(A) THE PROPORTION OF PARTICIPANTS ACHIEVING REMISSION OF INFLAMMATIONS AT OTHER SITES

Remission of inflammations at other sites was not reported in any of the studies, or inadequately¹⁶ (no separate data of the first randomised treatment regimen).

(B) INVESTIGATOR-ASSESSED CHANGE IN ENL SEVERITY

One study used a global assessment score to assess for changes in ENL symptoms (anorexia, arthralgias, chills, malaise, neuritis, orchitis and fever).¹⁷ One study used a grading scale (0–3) to assess changes in ENL severity, with higher grades indicating more severe ENL.²⁴ One study¹³ used an ENL severity score, but did not provide individual participant data or means and standard deviations for comparison. Two studies assessed change in ENL severity using different scoring methods, but provided only sum scores of the weekly scores over the 4 weeks trial period.^{14,19} One study assessed the frequency and severity of ENL, but did not provide data or significant test values for comparison.¹² One study reported control of reaction, but it was unclear how control was defined.²³ It was unclear whether any of the scales used had been formally validated.

Systemic corticosteroids

Change in ENL severity was not reported for any systemic corticosteroid interventions.

Systemic non-steroidal immunomodulatory therapies

Short-term: No significant difference in improvement (becoming asymptomatic) was found between the 100 mg thalidomide regimen and the 300 mg thalidomide regimen after 7 days of treatment (RR 1.67; 95% CI 0.85 to 3.26; $n = 22$).¹⁷

Medium-term: No significant difference in improvement (change from grade 3 to grade 1 or 0) was observed between levamisole and placebo after 3 months (RR 0.95; 95% CI 0.36 to

2.49; $n = 12$).²⁴ No significant difference in control of reaction was found between indomethacin and chloroquine (RR 0.95; 95% CI 0.52 to 1.74; $n = 23$), prednisolone (RR 0.65; 95% CI 0.41 to 1.02; $n = 24$) and aspirin (RR 0.89; 95% CI 0.51 to 1.55; $n = 25$) respectively. The duration of the trial and timing of outcome assessment was unclear; the paper stated both a trial period of 90 days and of 12 months.²³

(C) TIME TO NEXT CLINICAL EPISODE OF ENL

Time to next clinical episode of ENL was not reported in any of the studies. Four studies reporting differing definitions of time to next clinical episode of ENL. One study reported recurrence of new lesions by week 7 in participants who had achieved remission of existing ENL skin lesions at the end of the first week.¹⁷ One study reported relapse of ENL within 52 weeks after treatment.²⁰ Two studies reported recurrence of ENL by the end of the trial period in participants whose initial reaction was controlled in this same period.^{21,23}

Systemic corticosteroids

Time to next clinical episode of ENL was not reported for any systemic corticosteroid interventions.

Systemic non-steroidal immunomodulatory therapies

Medium-term: No significant difference in recurrence of new lesions after 7 weeks was observed between the 100 mg thalidomide regimen and the 300 mg thalidomide regimen (RR 3.75; 95% CI 0.62 to 22.64; $n = 13$).¹⁷ No significant difference in recurrence of ENL was found between clofazimine and prednisolone at the end of 12 weeks (RR 0.14; 95% CI 0.02 to 1.04; $n = 14$).²¹

Long-term: Results showed significantly less participants with relapse of ENL in the clofazimine group compared to the thalidomide group within 52 weeks after treatment (RR 0.08; 95% CI 0.01 to 0.56; $n = 72$).²⁰ No significant difference in recurrence of ENL was observed between indomethacin and chloroquine (RR 1.14; 95% CI 0.44 to 2.94; $n = 15$), prednisolone (RR 0.83; 95% CI 0.40 to 1.72; $n = 20$) or aspirin (RR 0.82; 95% CI 0.38 to 1.74; $n = 17$) respectively at the end of the trial period (90 days or 12 months).²³

(D) CHANGES IN QUALITY OF LIFE

None of the trials reported changes in quality of life.

ADVERSE EVENTS

Three trials did not report on adverse events.^{19,20,24} The other trials did provide information about adverse events, but often the number of participants with any adverse events in both groups was unclear.

Systemic corticosteroids

Minor adverse events not requiring withdrawal from treatment (swelling of the face, 'buffalo hump', striae distensae and acne) were more often reported in participants who received intravenous dextrose alone and oral steroids per their need to control ENL (control group) compared to those who received intravenous betamethasone in 5% dextrose, but the number of participants with adverse events in each group was not given.¹²

Systemic non-steroidal immunomodulatory therapies

Withdrawals from thalidomide treatment were caused by intestinal obstruction (1/12 participants),¹³ and worsening of ENL symptoms (3/22 participants).¹⁷ Minor adverse events not requiring withdrawal from thalidomide treatment (e.g. mild dermatitis, constipation, nausea, drowsiness, headache, insomnia, dizziness, dryness) were reported, but data for comparison was unclear or lacking.^{13-16,18} Significantly less participants in the 100 mg thalidomide regimen group reported any mild to moderate adverse events compared to those in the 300 mg thalidomide regimen group during the 7-week regimen (RR 0.46; 95% CI 0.23 to 0.93; $n = 22$).¹⁷ Withdrawals from pentoxifylline were due to gastrointestinal intolerance to the drug (1/24 participants) and fever and continuing lesion inflammation (3/24 participants). Adverse events not requiring withdrawal from pentoxifylline treatment (e.g. gastrointestinal complaints, nausea) were reported in 2/24 participants.¹⁸ Significantly more participants who received clofazimine had minor adverse events compared to those who received prednisolone (RR 1.92; 95% CI 1.10 to 3.35; $n = 24$). In the clofazimine group all participants had red/black pigmentation. No withdrawals from either clofazimine or prednisolone treatment were reported.²¹ Withdrawal from indomethacin treatment was due to deterioration of ENL (1/16 participants). Minor adverse events (e.g. nausea, dizziness, insomnia) were more frequently reported in participants who received indomethacin (9 events) compared to those who received prednisolone (1 event).²² No significant differences in minor adverse events (e.g. abdominal pain, nausea, headache) were observed between indomethacin and chloroquine (RR 1.09; 95% CI 0.57 to 2.10; $n = 23$), prednisolone (RR 0.92; 95% CI 0.52 to 1.63; $n = 24$) and aspirin (RR 2.23; 95% CI 0.87 to 5.71; $n = 25$) respectively.²³

Discussion

SUMMARY OF MAIN RESULTS

There are no good controlled trial data on the optimum treatment for controlling the acute phase of ENL. Our review included 13 randomised controlled trials involving 445 participants, and assessed the effects of betamethasone, thalidomide, pentoxifylline, clofazimine, indomethacin and levamisole in the management of ENL. One trial showed thalidomide treatment to be superior to acetylsalicylic acid treatment (less new reactions requiring further treatment) in the short-term control of ENL.¹⁶ Two trials showed significant longer-term benefits of clofazimine treatment compared to thalidomide (fewer recurrences) or prednisolone (more treatment successes) respectively.^{20,21} Mild to moderate adverse events were significantly higher in participants taking a 300 mg versus 100 mg dose of thalidomide¹⁷ and in participants taking clofazimine compared with prednisolone.²¹

The results should be considered with caution, due to methodological shortcomings. Data extraction of the study of Iyer *et al.* was limited to the results of the first randomised treatment regimen to avoid having more than one outcome per participant in the analysis.¹⁶ In another study participants continued on a maintenance dose of either 100 mg clofazimine or 50 mg thalidomide daily during the year after therapy. The study found significantly less recurrences of ENL in the group who received clofazimine therapy and this effect may be due to the persistence of clofazimine in the body over a longer period of time.²⁰ Karat *et al.* tapered the dose of prednisolone (starting at 30 mg daily and tapered off to 5 mg daily), while the dose of clofazimine (300 mg daily) remained the same during the 12-week treatment.²¹

QUALITY OF THE EVIDENCE

The quality of trials was generally poor, especially in studies published more than 20 years ago, due to the lack of clear reporting of methods, data and the allocation process. Most of the studies were too small (10 to 92 participants) to identify important differences even if they existed.

Three studies had a cross-over design which is associated with increased risk of bias.^{13,14,19} We therefore considered only results of the first phase treatment if these data were available. Two studies used more than one outcome of individual participants in the analysis.^{15,16} This may have led to an over-estimate of the effect because the within-patient variance between outcomes of the same person may be smaller than the between-patient variance of outcomes between individuals. We used only data of the first randomised treatment to overcome this concern and these were only available for the trial of Iyer *et al.*¹⁶ Most of the trials reported co-medication, which may have diluted the effect of the intervention tested in the studies. Most of the studies were not clear as to how allocation sequences were generated or how allocation was concealed. Blinding, especially of the outcome assessor, was not described at all or unclear. Trials assessing clofazimine were unblinded the moment skin discoloration appeared. This might have biased the outcome assessments. Six studies reported incomplete outcome data, but only two of those performed an intention to treat analysis. Baseline data were poorly reported and absent in five studies. Adverse effects were often reported inadequately, limiting comparisons between experimental and control groups.

Conclusion

IMPLICATIONS FOR PRACTICE

There is some evidence of benefit for thalidomide and clofazimine, but generally we found insufficient evidence to make any firm recommendations on the use of any of the interventions tested for management of ENL and included in this review. This does not mean they do not work, because the studies were generally of poor quality and small-sized.

Treatment with thalidomide showed a significant benefit compared to acetylsalicylic acid (aspirin). Clofazimine treatment was superior to prednisolone and thalidomide. Current guidelines for the management of ENL are given by bodies such as the World Health Organization (WHO) and the International Federation of Anti-Leprosy Associations (ILEP), but these guidelines are not supported by evidence from randomised controlled trials and are developed from practice.

Most of the studies reported adverse effects of treatment. Mild to moderate adverse events were significantly higher in participants taking a 300 mg versus 100 mg dose of thalidomide and in participants taking clofazimine compared with prednisolone. Only in a few instances withdrawal from treatment was required, but it was not always clear whether this was due to treatment or for another reason. Adverse effects of commonly used drugs, such as prednisolone, clofazimine and thalidomide are well-documented and should be kept in mind when prescribing drugs for ENL.

IMPLICATIONS FOR RESEARCH

The 13 trials included in this review were generally of poor methodological quality and have mostly been of short duration. A wide range of interventions were assessed, one trial evaluated betamethasone, five trials thalidomide, one trial pentoxifylline, three trials clofazimine, two trials indomethacin and one trial levamisole.

It was often unclear what the duration and severity of ENL was before the starting of treatment. Future studies should have clearer case definitions for ENL and we recommend that different durations of ENL (single acute episode, multiple acute episode or chronic) and different severity of ENL (mild or severe) be distinguished, as such subgroups may need different management of ENL.

Erythema nodosum leprosum is a complicated disease known for its unpredictability, its variable severity and duration, and its often chronic and recurrent nature. Although most agents may work similarly for controlling the acute symptoms of ENL, prevention of recurrences is far more difficult.

There is a need for good quality studies which follow the current standards for design and reporting of randomised controlled trials, and for large multi-centre studies to ensure that enough participants are enrolled.

None of the studies investigated whether the interventions improved quality of life of participants and only a few examined the long-term effects of interventions. There is a need for clearly defined outcome measures, both at short-term and longer-term. We would recommend that future studies include outcomes, such as absence of new tender erythematous subcutaneous skin lesions at completion of the ENL therapy, disappearance of ENL associated inflammation at other sites than the skin (such as iritis and arthritis) at completion of the ENL therapy, time to next clinical episode of ENL after completion of treatment, and quality of life measures.

It is recommended that internationally recognised and validated severity scales be developed so that results from different countries can be compared.

A trial comparing directly prednisolone and thalidomide has never been done, and is urgently needed.

Future studies should aim to assess the efficacy, safety and optimal regimens of prednisolone and thalidomide for severe ENL and clofazimine for mild ENL as well as other potentially beneficial therapies.

Acknowledgements

We would like to thank the Netherlands Leprosy Relief for financial support, the Cochrane Skin Group for advice and help, Taixiang Wu who interpreted a paper in Chinese, Brenda

Gomes and Marcos Virmond who interpreted papers in Portuguese, and Linda Lehman and Ben Naafs for their support in searching or clarifying original research.

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