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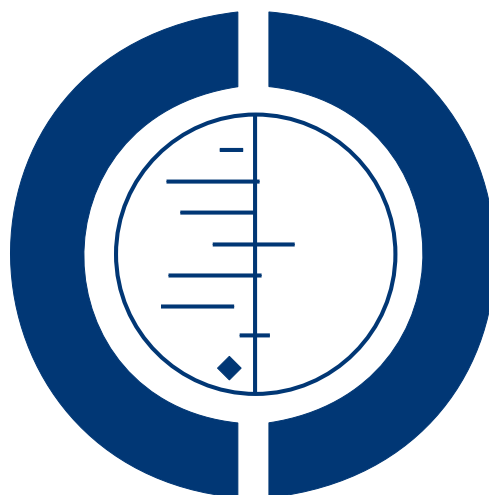
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Interventions for erythema nodosum leprosum (Review)

Van Veen NHJ, Lockwood DNJ, van Brakel WH, Ramirez Jr J, Richardus JH



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[Intervention Review]

Interventions for erythema nodosum leprosum

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ABSTRACT

Background

Erythema nodosum leprosum (ENL) is a serious immunological complication of leprosy, causing inflammation of skin, nerves, other organs, and general malaise. Many different therapies exist for ENL, but it is unclear if they work or which therapy is optimal.

Objectives

To assess the effects of interventions for erythema nodosum leprosum.

Search methods

We searched the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in *The 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 in March 2009. We checked reference lists of articles and contacted the American Leprosy Missions in Brazil to locate studies.

Selection criteria

Randomised controlled trials (RCTs) of interventions for ENL in people with leprosy.

Data collection and analysis

Two authors performed study selection, assessed trial quality, and extracted data.

Main results

We included 13 studies with a total of 445 participants. 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 remission of skin lesions compared to acetylsalicylic acid (aspirin) (RR 2.43; 95% CI 1.28 to 4.59) (1 trial, 92 participants). Clofazimine treatment was superior to prednisolone (more treatment successes; RR 3.67; 95% CI 1.36 to 9.91) (1 trial, 24 participants), and thalidomide (fewer recurrences; RR 0.08; 95% CI 0.01 to 0.56) (1 trial, 72 participants). We did not find any significant benefit for intravenous betamethasone compared to dextrose (1 trial, 10 participants), pentoxifylline compared to thalidomide (1 trial, 44 participants), indomethacin compared to prednisolone, aspirin or chloroquine treatments (2 trials, 80 participants), or levamisole compared to placebo (1 trial, 12 participants). Mild to moderate adverse events were significantly lower in participants taking 100 mg thalidomide compared to 300 mg thalidomide

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daily (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.

Authors' conclusions

There is some evidence of benefit for thalidomide and clofazimine, but generally we did not find clear evidence of benefit for interventions in the management of ENL. However, this does not mean they do not work, because the studies were small and poorly reported. Larger studies using clearly defined participants, outcome measures, and internationally recognised scales are urgently required.

PLAIN LANGUAGE SUMMARY

Interventions to treat erythema nodosum leprosum, a complication of leprosy

Leprosy remains a public health issue in poorer parts of the world. In 2007 there were approximately 255,000 new cases reported worldwide. Leprosy (or Hansen's disease) is a chronic infectious disease. The skin and peripheral nerves of people with leprosy contain leprosy bacteria. Leprosy can be cured with a combination of antibiotics. The immune system plays an important role in leprosy and determines if and how the disease will develop. The response of the immune system to the antigens of the leprosy bacteria may cause periods of inflammation in the skin and nerves, called reactions. Reactions are the main cause of acute nerve damage and disability in leprosy and occur in about one third of people with leprosy. One type of reaction is erythema nodosum leprosum (ENL), a serious and often chronic complication of leprosy caused by the immune system. People with ENL have red, painful swellings in the skin and often feel ill due to fever and general malaise. There are several treatments for ENL, including the oral drugs prednisolone, thalidomide, and clofazimine. We undertook a systematic review on this topic as it was not clear which treatments were most beneficial.

Our review included 13 randomised controlled trials involving 445 participants. These trials assessed: betamethasone (1 trial), thalidomide (5 trials), pentoxifylline (1 trial), clofazimine (3 trials), indomethacin (2 trials), and levamisole (1 trial). Generally, the quality of the studies was poor and many were too small to identify important clinical differences even if they existed. Three small trials showed benefit for thalidomide and clofazimine treatment in terms of fewer further reactions, more treatment successes, and less relapses of ENL.

Adverse events were reported in most of the trials, but it was often not possible to compare the occurrence of any adverse events between the experimental group and control group. Most adverse events reported were not too serious, and only a few participants could not complete treatment due to serious adverse events or for other reasons.

Whether the interventions improved the quality of life of participants, was not evaluated in any of the trials.

Although we did not find clear benefits in these series of small, poorly-performed studies, this does not mean that these drugs do not work in the treatment of ENL, only that scientific evidence is insufficient. Future studies should be better designed and use clear definitions and outcomes, including long-term outcomes and quality of life measures.

BACKGROUND

Description of the condition

Leprosy is a chronic infectious disease caused by the bacterium *Mycobacterium (M.) leprae*. Leprosy bacteria are spread as droplets from the nose of infected and untreated individuals (Barton 1974; Pedley 1976; Job 2008), but the importance of other routes of transmission is unclear. When the immune system fails to respond

effectively, the disease will develop. Often, the first sign of leprosy is a patch on the skin, but damage to peripheral nerves may occur as well (ILEP 2001). Leprosy develops in various clinical forms, dependent upon the response of the immune system. The internationally accepted Ridley-Jopling classification for leprosy recognises five different groups across a spectrum: tuberculoid (TT), borderline tuberculoid (BT), borderline (BB), borderline lepromatous (BL), and lepromatous (LL) (Ridley 1966). Across this spectrum, people with tuberculoid leprosy have a strong immune

response, only a few skin patches, and a low bacterial load, while people with lepromatous leprosy have no or very weak cell-mediated immunity for *M. leprae*, have many skin patches, and a high bacterial load. Most people have one of the borderline forms of leprosy: borderline tuberculoid (BT), mid-borderline (BB), or borderline lepromatous (BL). These forms are less easy to distinguish and less stable, meaning that one can shift from one form to another (Hastings 1988). An additional classification has been developed by the World Health Organization (WHO) and is based on the number of skin lesions only. People with five or less skin lesions are classified as having paucibacillary (PB) leprosy, while people with six or more skin lesions are classified as having multibacillary (MB) leprosy. This classification is often used in practice to decide what type of multiple-drug therapy (MDT) should be given to a person with leprosy (WHO 2000; Lockwood 2007). Leprosy infection can be treated effectively with a combination of antibiotics. Multiple-drug therapy (MDT) with the antibiotics rifampicin, dapsone, and clofazimine was introduced in the 1980s and is provided free by the World Health Organization (ILEP 2001; WHO 2006). Those with PB leprosy receive treatment (dapsone and rifampicin) for six months and those with MB leprosy are treated with dapsone, rifampicin, and clofazimine for 12 months (WHO 2003). Since the introduction of MDT, the number of people affected by leprosy has decreased substantially. At the beginning of 2008 the prevalence was about 213,000 worldwide. This is the registered number of people on MDT treatment. The number of people newly reported in 2007 was approximately 255,000 (WHO 2008).

The body's immune response to the leprosy bacillus may also cause so-called 'reactions'. There are two types of potentially nerve damaging reactions: type 1 reaction or reversal reaction, and type 2 reaction or erythema nodosum leprosum (ENL). Type 1, or reversal reaction, presents as acute inflammation in skin lesions and nerves. Erythema nodosum leprosum presents as new, red, painful and tender swellings in the skin, usually on the legs and arms, and sometimes on the trunk; it varies in severity. When the reaction is mild, only the skin is affected and there may be low-grade fever. When the reaction is severe, the swellings are multiple and may ulcerate, there may be high fever and other organs may be inflamed, such as the nerves, eyes, joints, testes, and lymph nodes. If neuritis is present, it is often less severe than neuritis resulting from type 1 reaction (ILEP 2002; Kahawita 2008). Most people with ENL have acute multiple episodes of ENL or chronic ENL over several years. Few people experience a single acute episode of ENL (Nery 1998; Saunderson 2000; Pocaterra 2006). Single acute ENL reaction can be defined as one ENL episode with no recurrence of ENL whilst receiving prednisolone, no increase in severity requiring an increased steroid dose, and no recurrence after the prednisolone has stopped. Acute multiple ENL reaction is defined as more than one ENL episode with the same characteristics as acute single ENL. Chronic ENL is defined as an episode lasting for more than six months. This could include single and multiple

episodes. Distinguishing and recognising these different types of ENL will be useful in individual management and treatment of ENL (Pocaterra 2006).

Erythema nodosum leprosum 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 percentage of people diagnosed with ENL differs between countries and studies. Countries in Asia and Brazil report high rates of ENL. A study from India found an overall ENL prevalence of 24% (Pocaterra 2006) and a study from Brazil reported an ENL rate of 31% among people on MB MDT treatment (Nery 1998). Studies that look at BL and LL subgroups rather than the whole MB leprosy group will give better estimations of ENL rates, because only these subgroups are at risk of developing ENL (Walker 2007). An Indian study found that almost 50% of people with LL and 9% of people with BL had ENL (Pocaterra 2006), and in a study from Ethiopia 12% of those with LL and 4% of those with BL developed ENL (Saunderson 2000). Erythema nodosum leprosum may occur before the start of treatment, but usually develops within the first three years after starting multiple-drug therapy (MDT). After completion of treatment, people may still have episodes of ENL for several years, because they have persisting mycobacterial antigens despite successful antibacterial treatment (ILEP 2002; Naafs 2003a).

Causes and risk factors

Erythema nodosum leprosum is an immune-mediated complication of leprosy. It is caused partly by deposition of *M. leprae* antigen and antibody complexes. These complexes circulate in the blood and may precipitate in tissue, particularly on the wall of small blood vessels, causing acute inflammation (vasculitis) and release of tissue-damaging enzymes in any organ or tissue invaded by the leprosy bacillus. In addition, the immune system activates cells (macrophages and T cells) that attack and kill the bacteria (Lockwood 1996; Naafs 2003b; Kahawita 2008). Risk factors for developing ENL are lepromatous classification, high bacterial loads, and being aged under 40 years (Manandhar 1999; Saunderson 2000; Kumar 2004).

Impact

People who have ENL usually feel ill (general malaise, fever) and many organs may be affected. Erythema nodosum leprosum is often a recurrent or chronic condition and requires treatment for a long period. Having repeated episodes of ill health, especially in people who are in an economically active period in their lives may cause a further burden. It may affect male fertility due to inflammation of the testis. Women are affected by having fewer treatment options in their childbearing years due to the side-effects of drugs such as thalidomide (Nery 1998; Saunderson 2000; Pocaterra 2006). Leprosy has a far more negative image than many

other diseases. Having visible signs of leprosy or side-effects from treatment triggers discrimination and stigmatisation (Heijnders 2004; Rafferty 2005). The psychological impact of a chronic and stigmatising condition may be profound.

Description of the intervention

Most therapies for ENL aim to control acute inflammation, relieving the pain and preventing further nerve damage or new episodes. Several treatments are available for ENL.

How the intervention might work

The conventional treatment for mild ENL is rest and anti-inflammatory medication to control the acute inflammatory skin lesions and fever. Aspirin is the most commonly used anti-inflammatory drug, but indomethacin, chloroquine, and colchicine have been tested as well. These different anti-inflammatory drugs have not been formally compared in mild ENL and there is no data to suggest that they are superior to aspirin (ILEP 1996; Lockwood 1996).

For severe ENL, prednisolone and clofazimine are most commonly used. Prednisolone usually acts rapidly by controlling the acute inflammation and relieving the pain, fever, and other signs. 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. Erythema nodosum leprosum 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 (ILEP 1996; Lockwood 1996).

Clofazimine is considered a useful anti-inflammatory drug when corticosteroids are contraindicated or need to be reduced (WHO). However, treatment with clofazimine usually takes four to six weeks to become active and the dose of clofazimine needed to control ENL is higher than the dose used in MDT (ILEP 1996). Disadvantages of continuous high doses of clofazimine are gastrointestinal symptoms (e.g. diarrhoea) and dark discolouration of the skin. These skin changes usually develop within a few weeks after starting clofazimine treatment and may take two or more years to disappear (ILEP 1996; Lockwood 1996).

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- α (tumour necrosis factor- α) but other mechanisms may contribute to its anti-inflammatory effect (Walker 2007). The seventh WHO Expert Committee on Leprosy considered thalidomide as an effective treatment of severe ENL, and recommended restriction of thalidomide treatment to male or postmenopausal female patients only. Thalidomide should only be given to women of childbearing age when comprehensive contra-

ceptive precautions can be taken, because its use may cause serious birth defects when taken in early pregnancy (WHO 1998).

Other therapies have been tested, such as ciclosporin, pentoxifylline, oral zinc, and *Mycobacterium w* vaccination (Uyemura 1986; Zaheer 1993; Mahajan 1994; Nery 2000). New therapies for other immune-mediated conditions seem promising. Examples are TNF- α antibody treatment, intravenous immunoglobulin, and tenidap (Lockwood 1996). TNF- α antibody treatment (infliximab) has been reported to be successful in the treatment of a single case of recurrent ENL (Faber 2006). However, the person relapsed and eventually required treatment with thalidomide (Faber, personal communication). It is plausible that these therapies may be effective for controlling ENL, but evidence from randomised controlled trials is very limited.

Why it is important to do this review

Erythema nodosum leprosum is a serious immunological complication of leprosy. The complex mechanisms underlying ENL are not yet fully understood, 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 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.

OBJECTIVES

To assess the effects of any therapy or treatment used in the management of ENL.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) of any design.

Types of participants

Anyone affected by leprosy with ENL, confirmed by appropriate clinical features. The definition of ENL is: '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 (Smith 2002; Van Brakel 2005).

Types of interventions

Any therapy for ENL, including:

(1) Systemic corticosteroids

- Oral therapies: prednisolone
- Intravenous therapies: betamethasone, methylprednisolone

(2) Systemic non-steroidal immunomodulatory therapies

- Immune modulators: thalidomide, ciclosporin, pentoxifylline
- Anti-inflammatory therapies: clofazimine, aspirin, chloroquine, colchicine, indomethacin

(3) Diverse therapies

- Oral zinc
- *Mycobacterium w* vaccine

The comparators were no treatment, placebo, usual care (e.g. systemic corticosteroid with or without pentoxifylline), or another listed therapy. We included trials which compared different dosages of the same therapy or different routes of administration (e.g. intravenous versus oral systemic corticosteroids).

Types of outcome measures

Primary outcomes

(a) 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 outcomes

(a) The proportion of participants achieving remission of inflammations at other sites

Remission was defined as the disappearance of inflammation associated with ENL at sites other than the skin (e.g. iritis, arthritis) at completion of the ENL therapy, as assessed by a clinician.

(b) Investigator-assessed change in ENL severity

The change in ENL severity, compared to baseline, using a grading scale as used in each of the studies.

(c) Time to next clinical episode of ENL

Time to next clinical episode of ENL was defined as the time between the last dose of ENL treatment and appearance of new signs of ENL reaction.

(d) Changes in quality of life

As assessed using a recognised instrument (generic, dermatology specific, disease specific, or patient-generated index).

Timing of outcome assessment

We considered data that had been recorded for four 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 four 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 (one to four weeks) was considered the primary endpoint, because the definite treatment effects should be visible within the first few weeks. The medium-term assessment (between four weeks and six months) was used as a secondary endpoint. Assessments of more than six months after the start of treatment were considered long-term outcomes.

Adverse outcomes

We were looking at a wide range of interventions and could not pre-specify which were the most important/common adverse events. Therefore we have documented the incidence and severity of all recorded local and systemic adverse events, at any time point, in all the included studies.

Economic data

Data relating to costs were not reported and we could not address cost implications in the discussion due to lack of data.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Skin Group Specialised Register on 11th March 2009 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.

We searched the Cochrane Central Register of Controlled Trials in *The Cochrane Library* (Issue 1, 2009) using the search strategy in [Appendix 1](#).

We searched MEDLINE (from 2003) on 11th March 2009 using the search strategy in [Appendix 2](#).

We searched EMBASE (from 2005) on 11th March 2009 using the search strategy in [Appendix 3](#).

The UK Cochrane Centre (UKCC) has an ongoing project to systematically search MEDLINE and EMBASE for reports of trials which are then included in the Cochrane Central Register of Controlled Trials. Searching has currently been completed in MEDLINE to 2003 and in EMBASE to 2005. Further searching has been undertaken for this review by the Cochrane Skin Group to cover the years that have not been searched by the UKCC.

We searched AMED (Allied and Complementary Medicine, from 1985) on 11th March 2009 using the search strategy [Appendix 4](#).

We searched LILACS (Latin American and Caribbean Health Science Information database, from 1982) on 11th March 2009 using the search strategy in [Appendix 5](#).

We searched CINAHL (from 1980) on 17th March 2009 using the search strategy in [Appendix 6](#).

Ongoing Trials

We searched for ongoing trials in the following ongoing trials registers on 17th March 2009 using the search terms 'leprosy', 'erythema nodosum leprosum' and 'type 2 reaction':

The metaRegister of Controlled Trials www.controlled-trials.com

The U.S. National Institutes of Health Ongoing Trials Register www.clinicaltrials.gov

The Australian and New Zealand Clinical Trials Registry www.anzctr.org.au

The World Health Organization International Clinical Trials Registry Platform www.who.int/trialsearch

The Ongoing Skin Trials register www.nottingham.ac.uk/ongoingskintrials

Searching other resources

Grey literature

We checked the conference proceeding from the International Leprosy Congress (2008) for RCTs and where appropriate the trial authors were contacted for further information.

Reference lists

We checked the references of the included studies, but did not identify any further trials.

Correspondence

Where possible we corresponded with trial authors of studies less than 15 years old about unpublished and ongoing trials. We contacted a technical consultant at the American Leprosy Missions in Brazil for reports of trials from Brazil.

Adverse effects

We did not do a separate search for adverse events, but we searched within the included studies.

Language restrictions

There were no language restrictions when we searched for publications. We sought translations of papers in languages other than English. Taixiang Wu interpreted a paper in Chinese, and Brenda Gomes and Marcos Virmond interpreted papers in Portuguese.

Data collection and analysis

Selection of studies

Two authors (NvV, JHR) checked the titles and abstracts identified from the searches. If it was clear that the study did not refer to a randomised controlled trial on erythema nodosum leprosum, it was excluded. If it was unclear, then the full text of the study was obtained for independent assessment by two authors (NvV, JHR). The authors decided which trials fitted the inclusion criteria. Any disagreement was resolved by discussion between the authors. It was not necessary to refer to a third author. We recorded excluded studies and reasons for exclusion in the [Characteristics of excluded studies](#) table.

Data extraction and management

One author (NvV) entered data onto a data extraction form and a second author (JHR) checked the data. The authors (NvV, JHR) discussed discrepancies between themselves. Missing data were obtained from trial authors where possible. One author (NvV) entered data into RevMan. The authors were not blinded to the names of trial authors, journals, or institutions.

For the participants' and investigators' global assessments of improvement, the authors translated reported changes in ENL severity into the proportion of participants with improvement greater than minimal. By improvement greater than minimal we meant anything greater than the first category of improvement on a Likert scale, or greater than 50% improvement from baseline on a continuous scale. For the purpose of calculating clinical efficacy, we regarded categories relating to greater than minimal improvement as a treatment success.

All other outcomes were expressed as the actual or percentage change from baseline.

Assessment of risk of bias in included studies

The quality assessment included an evaluation of the following components for each included study, since there is some evidence that these are associated with biased estimates of treatment effect (Juni 2001):

- (a) the method of generation of the randomisation sequence;
- (b) the method of allocation concealment - it was considered 'adequate' if the assignment could not be foreseen;
- (c) who was blinded/not blinded (participants, clinicians, outcome assessors);
- (d) how many participants were lost to follow-up in each arm (split into postrandomisation exclusion and later losses if possible) and whether participants were analysed in the groups to which they were originally randomised (intention-to-treat principle).

In addition, assessment was made of the following:

- (e) degree of certainty that participants have ENL;
- (f) baseline comparison for age, sex, duration, and severity of ENL;
- (g) whether outcome measures were described adequately.

The information is recorded in the risk of bias table under [Characteristics of included studies](#).

Measures of treatment effect

Dichotomous data

We expressed the results as risk ratio (RR) and 95% confidence intervals (CI) for dichotomous outcomes.

Continuous data

We expressed the results as differences in means (MD) and 95% CI for continuous outcomes. We did not use a standardised mean difference (SMD) since no continuous outcome measures could be combined.

Time-to-event data

We had no time-to-event data to summarise the log hazard ratio and 95% CI.

Unit of analysis issues

Cross-over trials

We analysed cross-over trials using data from the first phase only, but could not pool with parallel design studies due to lack of comparable studies or differences in timing of outcome assessment.

Studies with multiple treatment groups

Where there were multiple intervention groups within a trial, we made pairwise comparisons of similar ENL interventions or ENL active components versus no treatment, placebo, or another ENL intervention.

Other

We did not find any internally controlled trials. We excluded non-randomised controlled studies from the analyses but these were commented on in the Discussion section.

Dealing with missing data

We were not able to conduct an intention-to-treat analysis when participant drop-out led to missing data due to lack of information from trial authors. We contacted trial authors of studies less than 15 years old to provide missing statistics such as standard deviations, but they failed to respond or provide us with the missing data.

Assessment of heterogeneity

We did not assess statistical heterogeneity using the I^2 statistic, because there were no studies to be pooled.

Assessment of reporting biases

We did not perform funnel plots, because there were fewer than ten poolable studies.

Data synthesis

We did not perform a meta-analysis to calculate a weighted treatment effect across trials, using a random-effects model, because there were no studies with a similar type of ENL intervention or a similar active component. Instead, we summarised the data for each trial.

Subgroup analysis and investigation of heterogeneity

We did not perform further subgroup analysis due to lack of data on different subgroups. The groups were different severity of ENL (mild or severe) and different duration of ENL (single acute, multiple acute, or chronic).

Sensitivity analysis

We did not perform sensitivity analyses examining the effects of excluding study subgroups, e.g. those studies with low methodological quality, since no meta-analyses were performed.

Other

Where there was uncertainty, we contacted the trial authors for clarification. A consumer was part of the review team to ensure the relevance and readability of the final review.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

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 persons 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.

Included studies

We included 13 trials with 445 participants in this review and these are described in the [Characteristics of included studies](#) table. Ten studies were published between 1969 and 1985 and three studies between 2002 and 2007. The follow-up period varied from 7 days to 60 weeks in 13 trials and was unclear in 1 trial ([Karat 1969](#)).

Design

Three trials had a cross-over design ([Pearson 1969](#); [Helmy 1971](#); [Waters 1971](#)) and 10 trials had a parallel group design, of which 1 trial had 4 parallel groups ([Karat 1969](#)).

Sample sizes

The studies involved sample sizes between 9 and 92 participants. Two studies randomised and evaluated ENL reactions of participants ([Iyer 1971](#); [Sheskin 1969](#)).

Setting

Twelve studies were done in single centres in Brazil, India, Malaysia, Philippines, Singapore, and Venezuela. One study was conducted in multiple centres in India, Mali, Somalia, and Spain ([Iyer 1971](#)).

Participants

The age range of participants in 8 studies was 14 to 69 years, 5 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 to 12.5 years in 8 trials, and 5 trials did not report this information. The severity of reactions ranged from mild to severe and was reported in eight trials.

Interventions

The included studies examined several interventions.

Systemic corticosteroids:

- infusion of betamethasone in 5% dextrose versus infusion of 5% dextrose ([Girdhar 2002](#); parallel group).

Systemic non-steroidal immunomodulatory therapies:

- thalidomide versus placebo ([Pearson 1969](#); [Waters 1971](#): cross-over; [Sheskin 1969](#): parallel group);
- thalidomide versus acetylsalicylic acid ([Iyer 1971](#); parallel group);
- 100 mg thalidomide regimen versus 300 mg thalidomide regimen ([Villahermosa 2005](#); parallel group);
- pentoxifylline versus thalidomide ([Sales 2007](#); parallel group);
- clofazimine versus placebo ([Helmy 1971](#); cross-over);
- clofazimine versus thalidomide ([Iyer 1976](#); parallel group);
- clofazimine versus prednisolone ([Karat 1970](#); parallel group);
- indomethacin versus prednisolone ([Ing 1969](#); parallel group);
- indomethacin versus chloroquine versus prednisolone versus aspirin ([Karat 1969](#); parallel group);
- levamisole versus placebo ([Arora 1985](#); parallel group).

Diverse therapies:

- no trials assessing any other therapies were found.

Cointerventions were reported in 11 trials. These included iron for those with anaemia, anti-leprosy treatments (dapsone or MDT), analgesics (e.g. paracetamol, stibophen), steroids, and diuretics for treating oedema.

Outcomes

The primary outcome of remission of skin lesions, measured as the absence of new tender erythematous subcutaneous skin lesions at completion of the ENL therapy, was not explicitly reported in any of the trials. Two trials defined treatment success or improvement including the absence of new ENL lesions ([Sheskin 1969](#); [Karat 1970](#)). Three studies reported the resolution of existing skin lesions ([Ing 1969](#); [Villahermosa 2005](#); [Sales 2007](#)), and one study reported the number of participants with no further reaction after the first treatment regimen ([Iyer 1971](#)).

The secondary outcome of remission of inflammation at other sites was not explicitly reported in any of the trials. Seven trials used different grading scales or scores to assess ENL severity (Karat 1969; Pearson 1969; Helmy 1971; Waters 1971; Arora 1985; Girdhar 2002; Villahermosa 2005). The secondary outcome of time to next clinical episode was not reported in any of the trials, but four trials mentioned recurrence rates of reactions (Karat 1969; Karat 1970; Iyer 1976; Villahermosa 2005). None of the studies measured changes in quality of life.

Six trials recorded data only for four weeks or less from the start of treatment, reflecting short-term benefit (Ing 1969; Sheskin 1969; Helmy 1971; Iyer 1971; Waters 1971; Sales 2007). Three trials had the outcome assessment at medium-term, ranging from four weeks to six months from the start of treatment (Pearson 1969; Karat 1970; Arora 1985). One trial assessed long-term benefit, more than six months after treatment (Girdhar 2002). One trial assessed both short-term and medium-term (Villahermosa 2005), and one trial both medium-term and long-term (Iyer 1976). The timing of outcome assessment was unclear in one trial (Karat 1969).

Adverse effects were not reported in three trials (Arora 1985; Helmy 1971; Iyer 1976).

There was great diversity (or heterogeneity) between interventions and methods used to measure outcomes in the trials. None of the studies used similar interventions and comparisons which could be pooled.

Excluded studies

We excluded 35 studies and their details can be found in the [Characteristics of excluded studies](#) table. Of these 35 studies, 21 were not RCTs, 2 were excluded as they did randomisation by alternation, 10 did not have ENL as inclusion criterion but included participants with lepromatous leprosy in general, 1 was a duplicate study, and 1 was excluded because it described only intake results and was not completed.

Ongoing studies

We found one ongoing randomised, single-blind trial examining montelukast in ENL reaction, compared to prednisolone. Enrollment started in December 2006 and took 18 months. Outcome assessment was scheduled 24 weeks after starting treatment.

Risk of bias in included studies

The Collaboration's recommended tool for assessing risk of bias was used (Higgins 2008), the methodological quality of the trials was generally poor. Since no meta-analyses were performed, sensitivity analysis based on methodological quality was not performed. Three trials had a cross-over design (Pearson 1969; Helmy 1971; Waters 1971). The main concerns associated with cross-over trials

are: (i) whether the cross-over design is suitable; (ii) whether there is a carry-over effect; (iii) whether only first period data are available; (iv) incorrect analysis; and (v) comparability of results with those from parallel-group trials. None of the trials had a wash-out period between the two interventions, which might have caused a possible carry-over effect, especially in the trial assessing clofazimine that can persist in the body for a long time. We analysed these trials using data from the first phase only if these were available to overcome these concerns.

Two trials evaluated reactions of participants (Sheskin 1969; Iyer 1971). Participants received up to four treatment regimens for each reaction during the trials. This may have led to an overestimate 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 if these were available to overcome this concern.

Allocation

None of the trials were clear on how randomisation lists were generated. In two of the trials, the trial authors have clearly reported that concealment of allocation was adequate; both studies had the medication pre-prepared by a drug company (Iyer 1971; Villahermosa 2005).

Blinding

Blinding of outcome assessment was attempted for most of the trials. However, the method as to how this was done was generally unclear and poorly described. None of the studies clearly described who (the participants, clinicians, and outcome assessors) was blinded. One trial was an open trial (Iyer 1976); this was a trial with clofazimine, which is known to give skin discolouration.

Incomplete outcome data

Information about incomplete outcome data was generally not reported and participant loss to follow-up 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% (Karat 1969; Sheskin 1969; Karat 1970; Iyer 1971; Waters 1971; Iyer 1976; Arora 1985). Two trials with missing outcome data performed intention-to-treat analysis (Pearson 1969; Sales 2007). Two trials (Ing 1969; Girdhar 2002) had participant losses (1/30 participants and 1/10 participants respectively), but it was not clear as to whether intention-to-treat analysis was done. Two trials (Helmy 1971; Villahermosa 2005) with incomplete outcome data (5/15 participants and 1/22 participants respectively) did not perform an intention-to-treat analysis.

Selective reporting

Six trials did not perform a statistical analysis, but only described the results (Ing 1969; Pearson 1969; Helmy 1971; Iyer 1971; Waters 1971; Iyer 1976). One study (Ing 1969) reported in the summary that “indomethacin is effective in treating only mild and moderate cases of ENL”. The summary of one study (Waters 1971) concluded that “nine of the ten participants showed a very significant reduction in steroid requirement”. Another study (Pearson 1969) summarised that “thalidomide was superior to a placebo”. None of these studies provided sufficient evidence (e.g. significant test values) to support these claims.

Other potential sources of bias

Certainty of diagnosis

Five studies specified erythema nodosum leprosum (ENL) in their inclusion criteria (Sheskin 1969; Karat 1970; Iyer 1971; Villahermosa 2005; Sales 2007). Most other studies did not define ENL, but did mention it under the inclusion criteria.

Baseline comparison for age, sex, duration and severity of ENL

Five studies did not provide data for baseline comparison (Karat 1969; Pearson 1969; Helmy 1971; Iyer 1971; Girdhar 2002). Five studies reported some baseline data, but it was unclear whether groups were similar at baseline (Ing 1969; Sheskin 1969; Waters 1971; Iyer 1976; Arora 1985). Two studies reported only two (age and sex) (Sales 2007) or three (age, sex, and duration of ENL) (Villahermosa 2005) of the characteristics being similar in both groups. In one study, all baseline characteristics (age, sex, duration, and severity of ENL) were similar in both groups (Karat 1970).

Explicit outcome measures

Six studies did not clearly describe outcome measures (Karat 1969; Pearson 1969; Helmy 1971; Iyer 1971; Iyer 1976; Arora 1985). The other studies did explicitly mention outcome measures, such as change in ENL severity, improvement, and treatment success.

Effects of interventions

Please see table of [Characteristics of included studies](#). 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 therapies as listed under diverse therapies.

Timing of outcome assessment

Results have been grouped according to the timing of outcome assessment: short-term (one to four weeks), medium-term (between four weeks and six months), and long-term (more than six months).

Economic data

None of the trials reported economic outcome data.

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 1970 reported treatment success, including absence of new ENL lesions, and Sheskin 1969 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 (Iyer 1971). Three studies reported the resolution of existing skin lesions (Ing 1969; Villahermosa 2005; Sales 2007).

Systemic corticosteroids

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

Systemic non-steroidal immunomodulatory therapies

Short-term:

Significantly more participants who received thalidomide treatment had no further reaction after seven 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; [Analysis 1.1](#)) (Iyer 1971). 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 seven days (RR 1.33; 95% CI 0.64 to 2.79; n=22; [Analysis 2.1](#)) (Villahermosa 2005). 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; [Analysis 3.1](#)) ([Sales 2007](#)). No significant difference in remission of existing ENL lesions was found between indomethacin and prednisolone after four weeks (RR 2.33; 95% CI 0.76 to 7.13; n=30; [Analysis 6.1](#)) ([Ing 1969](#)).

Medium-term:

One participant, who had received the 300 mg thalidomide regimen, had a successful taper, defined as a complete response after seven days and lack of new acutely inflamed lesions during the six-week taper and for at least two months after stopping thalidomide ([Villahermosa 2005](#)). Significantly 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; [Analysis 4.1](#)) ([Karat 1970](#)).

Secondary outcome measures

(a) The proportion of participants achieving remission of inflammation at other sites

Remission of inflammations at other sites was not reported in any of the studies. In [Iyer 1971](#), the data was reported inadequately as there was no separate data from 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) ([Villahermosa 2005](#)). One study used a grading scale (0 to 3) to assess changes in ENL severity, with higher grades indicating more severe ENL ([Arora 1985](#)). One study ([Pearson 1969](#)) 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 four-week trial period ([Helmy 1971](#); [Waters 1971](#)). One study assessed the frequency and severity of ENL, but did not provide data or significant test values for comparison ([Girdhar 2002](#)). One study reported control of reaction, but it was unclear how control was defined ([Karat 1969](#)). 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 seven days of treatment (RR 1.67; 95% CI 0.85 to 3.26; n=22; [Analysis 2.2](#)) ([Villahermosa 2005](#)).

Medium-term:

No significant difference in improvement (change from grade 3 to grade 1 or 0) was observed between levamisole and placebo after three months (RR 0.95; 95% CI 0.36 to 2.49; n=12; [Analysis 9.1](#)) ([Arora 1985](#)). 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; [Analysis 7.1](#)), prednisolone (RR 0.65; 95% CI 0.41 to 1.02; n=24; [Analysis 6.2](#)) or aspirin (RR 0.89; 95% CI 0.51 to 1.55; n=25; [Analysis 8.1](#)) 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 ([Karat 1969](#)).

(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 reported differing definitions of time to next clinical episode of ENL. One study reported recurrence of new lesions by week seven in participants who had achieved remission of existing ENL skin lesions at the end of the first week ([Villahermosa 2005](#)). One study reported relapse of ENL within 52 weeks after treatment ([Iyer 1976](#)). Two studies reported recurrence of ENL by the end of the trial period in participants whose initial reaction was controlled in this same period ([Karat 1969](#); [Karat 1970](#)).

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 seven 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; [Analysis 2.3](#)) ([Villahermosa 2005](#)). 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; [Analysis 4.2](#)) ([Karat 1970](#)).

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; [Analysis 5.1](#)) ([Iyer 1976](#)). 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; [Analysis 7.2](#)), prednisolone (RR 0.83; 95% CI 0.40 to 1.72; n=20; [Analysis 6.3](#)) or aspirin (RR 0.82; 95% CI 0.38 to 1.74; n=17; [Analysis 8.2](#)) respectively at the end of the trial period (90 days or 12 months) ([Karat 1969](#)).

(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 ([Helmy 1971](#); [Iyer 1976](#); [Arora 1985](#)). 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 ([Girdhar 2002](#)).

Systemic non-steroidal immunomodulatory therapies

Withdrawals from thalidomide treatment were caused by intestinal obstruction (1/12 participants) ([Pearson 1969](#)), and worsening of ENL symptoms (3/22 participants) ([Villahermosa 2005](#)). 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 often unclear or lacking ([Pearson 1969](#); [Sheskin 1969](#); [Iyer 1971](#); [Waters 1971](#); [Sales 2007](#)). 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 seven-week regimen (RR

0.46; 95% CI 0.23 to 0.93; n=22; [Analysis 2.4](#)) ([Villahermosa 2005](#)). 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 ([Sales 2007](#)). 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; [Analysis 4.3](#)). In the clofazimine group all participants had red/black pigmentation. No withdrawals from either clofazimine or prednisolone treatment were reported ([Karat 1970](#)). 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) ([Ing 1969](#)). 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; [Analysis 7.3](#)), prednisolone (RR 0.92; 95% CI 0.52 to 1.63; n=24; [Analysis 6.4](#)) and aspirin (RR 2.23; 95% CI 0.87 to 5.71; n=25; [Analysis 8.3](#)) respectively ([Karat 1969](#)).

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) ([Iyer 1971](#)) in the short-term control of ENL. Two trials showed significant longer-term benefits of clofazimine treatment compared to thalidomide (fewer recurrences) or prednisolone (more treatment successes) respectively ([Karat 1970](#); [Iyer 1976](#)). Mild to moderate adverse events were significantly higher in participants taking a 300 mg versus 100 mg dose of thalidomide ([Villahermosa 2005](#)) and in participants taking clofazimine compared with prednisolone ([Karat 1970](#)).

The results should be considered with caution, due to methodological shortcomings. Data extraction of the study of [Iyer 1971](#) was limited to the results of the first randomised treatment regimen to avoid having more than one outcome per participant in the analysis. In the study of [Iyer 1976](#) 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 clo-

fazimine therapy and this effect may be due to the persistence of clofazimine in the body over a longer period of time. Karat 1970 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.

Overall completeness and applicability of evidence

The studies identified were not sufficient to address all of the objectives of the review. Two studies had outcome measures that were considered to reflect our primary outcome measure (Sheskin 1969; Karat 1970). Three studies assessed the disappearance of existing ENL skin lesions rather than the absence of new ENL skin lesions at the end of the therapy (Ing 1969; Villahermosa 2005; Sales 2007), and one study reported no further reactions after the first treatment regimen (Iyer 1971). None of the studies reported adequately on the secondary outcome measure: remission of inflammation at other sites upon completion of the ENL therapy, as assessed by a clinician. Seven studies assessed changes in ENL severity using a self-defined definition, scale, or score (Karat 1969; Pearson 1969; Helmy 1971; Waters 1971; Arora 1985; Girdhar 2002; Villahermosa 2005). None of the studies reported on the secondary outcome or time to next clinical episode, but four studies recorded recurrences of ENL in participants whose initial reaction was controlled (Karat 1969; Karat 1970; Iyer 1976; Villahermosa 2005). Adverse events were reported in all but three studies (Helmy 1971; Iyer 1976; Arora 1985). None of the studies assessed the effect of the intervention on quality of life of participants. The studies did not provide separate data for different subgroups, such as disease severity (mild or severe) or duration (single acute, multiple acute, or chronic), while this could have given useful information on effectiveness of treatment for different types of ENL. The results of the studies do not allow any robust conclusion regarding the general applicability of any of the interventions tested.

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 (Pearson 1969; Helmy 1971; Waters 1971). We therefore considered only the first phase treatment. Two studies used more than one outcome of individual participants in the analysis (Sheskin 1969; Iyer 1971). 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 over-

come this concern and these were only available for the trial of Iyer 1971. Most of the trials reported comedication, 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 discolouration 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.

Potential biases in the review process

The search process was elaborate and to our knowledge no other randomised controlled trials were available for this review. It is possible that not all relevant studies have been included in this review, and that we failed to find some unpublished trials. We contacted several people, but did not identify any new trials. The quality of reporting was generally poor and this may have led to misunderstandings during the critical appraisal of the studies. We contacted authors of studies less than 15 years old, but had poor response to requests for additional information. We were unable to assess for publication bias as there were not enough studies to perform a funnel plot. Most studies were small and showed no significant effect and we considered publication bias in this case not very likely. Some studies, assessing interventions for people with lepromatous leprosy and containing potentially useful data, had to be excluded because no separate results for people with ENL were reported.

Agreements and disagreements with other studies or reviews

A few systematic reviews on interventions for ENL have been found, but these focused on thalidomide and included non-randomised studies (Penna 2005; Walker 2007). These reviews concluded that although beneficial effects of thalidomide treatment were found, the evidence is limited due to methodological differences between studies and the use of thalidomide is restricted because of possible serious adverse effects such as teratogenicity, neuropathy, and thromboembolisms.

AUTHORS' CONCLUSIONS

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. In only a few instances was withdrawal from treatment 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 in the 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 inflammation associated with ENL at sites other than the skin (such as iritis and arthritis) at completion of the ENL therapy, as well as 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.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Arora 1985

Methods	Design: parallel group
Participants	Setting: single centre, hospital, India Incl: participants with ENL Excl: not stated M/F: 11/1 Age: 14 to 55 Duration: 0 to 7 years Severity: severe Randomised: 12 participants Evaluable: 12 participants Unit of analysis: individual
Interventions	Experimental group (n=5): levamisole capsules (150 mg daily) on 3 consecutive days repeating every fortnight for 3 months Control group (n=7): placebo capsules (dose unknown, daily) on 3 consecutive days repeating every fortnight for 3 months Other therapy: iron for anaemic participants
Outcomes	Improvement, defined as complete recovery from reaction, after 3 months
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided
Allocation concealment?	Unclear risk	Unclear, though states 'coding of drugs was done by other person and decoding at end of study'
Blinding? All outcomes	Unclear risk	Unclear who were blinded, though states trial was double-blind
Incomplete outcome data addressed? All outcomes	Unclear risk	No mention of attrition in text or tables, suggesting 100% follow-up
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	Not clear as to whether groups were similar at baseline; outcome measures not well-described

Girdhar 2002

Methods	Design: parallel group
Participants	Setting: single centre, leprosy centre, India Incl: lepromatous leprosy with 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) Unit of analysis: individual
Interventions	Experimental group (n=4): infusion of betamethasone in 5% dextrose daily for 3 days every 4 weeks for 6 months Control group (n=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
Outcomes	Change in severity and frequency of ENL 6 months after end of treatment Steroid requirement Side-effects
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided
Allocation concealment?	Unclear risk	No information provided
Blinding? All outcomes	Unclear risk	No information provided
Incomplete outcome data addressed? All outcomes	Unclear risk	No information provided
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	No information about baseline characteristics of both groups

Helmy 1971

Methods	Design: cross-over	
Participants	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 to 67 Duration: 6 months to 2 years Severity: moderately severe ENL Randomised: 15 participants Evaluable: 10 participants (5 lost to follow-up) Unit of analysis: individual	
Interventions	Group A (n=3): clofazimine capsules (100 mg 3 times daily) in weeks 1 to 4, followed by placebo capsules (dose unknown, 3 times daily) in weeks 5 to 8 Group B (n=7): placebo capsules (100 mg 3 times daily) in weeks 1 to 4, followed by clofazimine capsules (dose unknown, 3 times daily) in weeks 5 to 8 Other therapy: dapsone (100 mg 2 times daily); stibophen if needed; paracetamol issued twice weekly to be taken freely	
Outcomes	Severity score of ENL	
Notes	The trial consisted of a first control period (2 weeks), first trial period (4 weeks), second trial period (4 weeks), second control period (4 weeks)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided
Allocation concealment?	Unclear risk	Unclear, though states "key of drug allocation was kept in sealed envelope and opened only after analysis of the results"
Blinding? All outcomes	Unclear risk	Participant & clinician: no, outcome assessor: unclear. Trial was designed to be double-blind, but it ceased when discolouration due to clofazimine appeared
Incomplete outcome data addressed? All outcomes	High risk	5 participants lost to follow-up and excluded from analysis
Free of selective reporting?	Unclear risk	No statistical analysis performed
Free of other bias?	Unclear risk	No information about baseline characteristics of both groups; outcome measures not well-described

Ing 1969

Methods	Design: parallel group
Participants	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 Unit of analysis: individual
Interventions	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
Outcomes	Improvement after 4 weeks (e.g. mean change in pain relief, subsidence of lesions) Side-effects
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided
Allocation concealment?	Unclear risk	No information provided
Blinding? All outcomes	Unclear risk	No information provided
Incomplete outcome data addressed? All outcomes	Unclear risk	Not clear as to whether participant who did not complete treatment was included in analysis
Free of selective reporting?	High risk	No statistical evidence, though states "indomethacin is effective in treating only mild and moderate cases of ENL"
Free of other bias?	Unclear risk	Not clear as to whether groups were similar at baseline

Iyer 1971

Methods	Design: parallel group
Participants	Setting: multicentre, 4 centres, India, Mali, Somalia, Spain Incl: clearly demonstrable dermatological signs of acute lepra reactions i.e. erythema nodosum-like lesions or erythema multiforme-like lesions Excl: severe or life-threatening lepra reactions M/F: 92 M Age: 15 to 55+ Duration: not stated Severity: not stated Randomised: 214 ENL reactions (of 92 participants) Evaluable: 214 ENL reactions Unit of analysis: reaction
Interventions	Experimental group (n=116): thalidomide tablets (100 mg 4 times daily if ≥ 50 kg, or 100 mg 1 to 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 to 3 times daily if < 50 kg) for 7 days Other therapy: upon admission all drug therapy had to be ceased
Outcomes	No further reactions Changes in temperature, skin lesions, blood pressure, pulse rate, and blood cell count after 7 days Side-effects
Notes	Each reaction was treated with a 7-day regimen. A new regimen was allocated to a participant if there was no improvement or if new acute reactions occurred. The statistical design provided for treatment of 4 reactions in each participant, 2 with acetylsalicylic acid, and 2 with thalidomide, the order being random

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided
Allocation concealment?	Low risk	Confidential master sheet of drug allocation kept by WHO, bottles with tablets labelled by drug manufacturer according to master sheet
Blinding? All outcomes	Unclear risk	Unclear who were blinded, though states trial was double-blind
Incomplete outcome data addressed? All outcomes	Unclear risk	No mention of attrition in text or tables, suggesting 100% follow-up
Free of selective reporting?	Unclear risk	No statistical analysis performed

Iyer 1971 (Continued)

Free of other bias?	Unclear risk	No information about baseline characteristics of both groups; outcome measures not well-described
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Iyer 1976

Methods	Design: parallel group
Participants	Setting: single centre, India Incl: male, lepromatous leprosy and prone to recurrent reactive episodes Excl: not stated M/F: 72 M Age: 15 to 54 Duration: < 6 months to > 4 years Severity: moderate, severe Randomised: unclear, states "72 participants available for analysis" Evaluable: 72 participants Unit of analysis: individual
Interventions	Experimental group (n=36): clofazimine (100 mg 3 times daily) for 8 weeks, clofazimine (100 mg once a day) for 52 weeks Control group (n=36): thalidomide (100 mg 3 times daily) for 8 weeks, thalidomide (25 to 50 mg once a day) for 52 weeks Other therapy: dapsone (10 mg/kg/week) during 52 weeks maintenance therapy
Outcomes	Time-to-control reaction Maintenance of anti-reaction effect after therapy
Notes	First 8 weeks (part A) was acute treatment to control reaction as quickly and effectively as possible. Part B (52 weeks) was dosage aimed at maintaining effect

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided
Allocation concealment?	Unclear risk	No information provided
Blinding? All outcomes	High risk	No, open trial, blinding impossible due to skin discolouration from clofazimine
Incomplete outcome data addressed? All outcomes	Unclear risk	No mention of attrition in text or tables, suggesting 100% follow-up
Free of selective reporting?	Unclear risk	No statistical analysis performed

Iyer 1976 (Continued)

Free of other bias?	Unclear risk	Not clear as to whether groups were similar at baseline; outcome measures not well-described
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Karat 1969

Methods	Design: parallel group
Participants	<p>Setting: single centre, leprosy centre, India</p> <p>Incl: lepromatous leprosy with ENL, > 12 years</p> <p>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</p> <p>M/F: not stated</p> <p>Age: not stated</p> <p>Duration: not stated</p> <p>Severity: 28 mild, 22 severe</p> <p>Randomised: 50 participants</p> <p>Evaluable: 50 participants</p> <p>Unit of analysis: individual</p>
Interventions	<p>Group 1 (n=11): indomethacin orally (50 mg 3 times daily) in week 1 to 2, (25 mg 3 times daily) in week 3, (25 mg once a day) maintenance</p> <p>Group 2 (n=12): chloroquine orally (250 mg 3 times daily) in week 1 to 2, (250 mg 2 times daily) in week 3, (250 mg once a day) maintenance</p> <p>Group 3 (n=13): prednisolone orally (5 mg 3 times daily) in week 1 to 2, (5 mg 2 times daily) in week 3, (5 mg once a day) maintenance</p> <p>Group 4 (n=14): aspirin orally (1 g 3 times daily) in week 1 to 2, (1 g 2 times daily) in week 3, (500 mg 2 times daily) maintenance</p> <p>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</p>
Outcomes	<p>Control of reaction</p> <p>Recurrence of reaction</p> <p>Side-effects</p>
Notes	Duration of trial period unclear, paper states both trial period of 90 days and 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Unclear, though states "statistically randomised grouping"
Allocation concealment?	Unclear risk	Unclear, though states was confidential list
Blinding? All outcomes	Unclear risk	Unclear who were blinded, though states trial was double-blind

Karat 1969 (Continued)

Incomplete outcome data addressed? All outcomes	Unclear risk	No mention of attrition in text or tables, suggesting 100% follow-up
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	No information about baseline characteristics of both groups; outcome measures not well-described

Karat 1970

Methods	Design: parallel group
Participants	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 to 150 months Severity: severe Randomised: 24 participants Evaluable: 24 participants Unit of analysis: individual
Interventions	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) weeks 5 to 12 Other therapy: none
Outcomes	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 Recurrence of reaction during trial Side-effects
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Unclear, though states "list of random allocations"
Allocation concealment?	Unclear risk	Unclear, though states "list was prepared earlier and kept confidential at pharmacy"

Karat 1970 (Continued)

Blinding? All outcomes	Unclear risk	Unclear who were blinded, though states trial was double-blind
Incomplete outcome data addressed? All outcomes	Unclear risk	No mention of attrition in text or tables, suggesting 100% follow-up
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	

Pearson 1969

Methods	Design: cross-over
Participants	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) Unit of analysis: individual
Interventions	Group A (n=not stated): thalidomide tablets (100 mg 3 times daily) for 6 weeks, followed by placebo (dose and frequency unknown) for 6 weeks Group B (n=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
Outcomes	Change in ENL score Steroid requirement Side-effects
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided
Allocation concealment?	Unclear risk	No information provided
Blinding? All outcomes	Unclear risk	Participant & clinician: yes, outcome assessor: unclear

Pearson 1969 (Continued)

Incomplete outcome data addressed? All outcomes	Low risk	Intention-to-treat analysis performed; average scores for first 3 weeks of thalidomide have been inserted for weeks 10 to 12
Free of selective reporting?	High risk	No statistical evidence, though states "thalidomide was superior to a placebo"
Free of other bias?	Unclear risk	No information about baseline characteristics of both groups; outcome measures not well-described

Sales 2007

Methods	Design: parallel group
Participants	Setting: single centre, leprosy centre, Brazil Incl: MB leprosy, males between 18 to 60 years old, 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 to 69 Duration: not stated Severity: not stated Randomised: 44 participants Evaluable: 44 participants (8 lost to follow-up) Unit of analysis: individual
Interventions	Group A (n=24): pentoxifylline (1.2 g daily) for 30 days Group B (n=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
Outcomes	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 Side-effects
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided
Allocation concealment?	Unclear risk	No information provided

Sales 2007 (Continued)

Blinding? All outcomes	Unclear risk	Unclear who were blinded, though states trial was double-blinded
Incomplete outcome data addressed? All outcomes	Low risk	Intention-to-treat analysis performed; participants removed from trial were categorised as treatment non-responders
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	Unclear if all relevant baseline characteristics were similar

Sheskin 1969

Methods	Design: parallel group
Participants	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 to 58 Duration: 3 months to 9 years Severity: not stated Randomised: 173 ENL reactions (of 52 participants) Evaluable: 173 ENL reactions Unit of analysis: reaction
Interventions	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 adrenocorticotrophic hormone (ACTH) for prolonged periods at admission, same dosage was continued
Outcomes	Total improvement, defined as all dermatologic manifestations in advanced state of remission, no new elements, disappearance of characteristic lepra reaction symptoms after 7 days Side-effects
Notes	Each reaction was treated with a 7-day regimen. A new regimen was allocated to a participant if there was no improvement. Up to 4 consecutive treatment regimens were given to each participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided

Sheskin 1969 (Continued)

Allocation concealment?	Unclear risk	Unclear, though states “code unknown to investigators and kept elsewhere”
Blinding? All outcomes	Unclear risk	Unclear who were blinded, though states trial was double-blind
Incomplete outcome data addressed? All outcomes	Unclear risk	No mention of attrition in text or tables, suggesting 100% follow-up
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	Not clear as to whether groups were similar at baseline

Villahermosa 2005

Methods	Design: parallel group
Participants	<p>Setting: single centre, leprosy centre, Philippines</p> <p>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</p> <p>Excl: incapacitating ENL (bed ridden), severe neuritis, thalidomide ingestion within 30 days or corticosteroid ingestion within 2 weeks of enrollment</p> <p>M/F: 22 M</p> <p>Age: 18 to 46</p> <p>Duration: 0 to 3 years</p> <p>Severity: not stated</p> <p>Randomised: 22 participants</p> <p>Evaluable: 19 (3 lost to follow-up)</p> <p>Unit of analysis: individual</p>
Interventions	<p>Group A (n=12): thalidomide capsules, 100 mg daily (2x 50 mg, 4x dummy capsules) in week 1, 50 mg daily (1x 50 mg, 3x dummy capsules) in week 2 to 3, 4x dummy capsules daily in weeks 4 to 7</p> <p>Group B (n=10): thalidomide capsules, 300 mg daily (6x 50 mg, 0x dummy capsules) in week 1, 200 mg daily (4x 50 mg, 0x dummy capsules) in week 2 to 3, 100 mg daily (2x 50 mg, 2x dummy capsules) in week 4 to 5, 50 mg daily (1x 50 mg, 3x dummy capsules) in week 6 to 7</p> <p>Other therapy: acetaminophen for participants with fever during first 72 hours of study</p>
Outcomes	<p>Resolution of inflamed ENL nodules during initial 7-day treatment</p> <p>Global assessment</p> <p>Re-emergence of skin lesions during taper</p> <p>Week 7 lesion counts</p> <p>Recurrence of lesions after taper</p> <p>Safety and adverse events</p>

Villahermosa 2005 (Continued)

Notes	Week 1 treatment was acute treatment. Participants with complete or partial responses at week 1 were tapered from thalidomide during weeks 2 to 7	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided
Allocation concealment?	Low risk	Adequate, coded blister packs by pharmaceutical company
Blinding? All outcomes	Unclear risk	Participant: yes, clinician & outcome assessor: unclear; though states was double-blind
Incomplete outcome data addressed? All outcomes	High risk	Three participants withdrawn from trial and excluded from analysis
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	Unclear if all relevant baseline characteristics were similar

Waters 1971

Methods	Design: cross-over
Participants	<p>Setting: single centre, leprosy centre, Malaysia</p> <p>Incl: not stated, but included were participants with lepromatous leprosy and histologically confirmed moderately severe or severe chronic ENL</p> <p>Excl: not stated</p> <p>M/F: 10 M</p> <p>Age: 19 to 56</p> <p>Duration: 9 months to 3.5 years</p> <p>Severity: moderately severe or severe chronic ENL</p> <p>Randomised: 9 participants for first 16-week trial, 8 participants for second 24-week trial</p> <p>Evaluable: 9 participants for first 16-week trial, 8 participants for second 24-week trial</p> <p>Unit of analysis: individual</p>
Interventions	<p>16-week trial (n=9) and 24-week trial (n=8):</p> <p>Group A (n=5 or n=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</p> <p>Group B (n=4 or n=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</p> <p>Other therapy: 100 mg dapsone twice weekly, prednisolone or corticotrophin daily, mild analgesics if needed</p>

Waters 1971 (Continued)

Outcomes	Steroid requirement during trial period ENL score (temperature, severity)	
Notes	First trial lasted 16 weeks (4 weeks control, 4 weeks A, 4 weeks B, 4 weeks control). The second trial started 11 weeks after completion of first trial. The trial lasted 24 weeks (6 weeks control, 6 weeks A, 6 weeks B, 6 weeks control) and included 8 participants of which 7 participated in the first trial	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information provided
Allocation concealment?	Unclear risk	Unclear, though states "the code of drug allocation was not revealed to anyone until after the trial was completed"
Blinding? All outcomes	Unclear risk	Participant & clinician: yes, outcome assessor: unclear
Incomplete outcome data addressed? All outcomes	Unclear risk	No mention of attrition in text or tables, suggesting 100% follow-up
Free of selective reporting?	High risk	No statistical evidence, though states "nine of the ten participants showed a very significant reduction in steroid requirement"
Free of other bias?	Unclear risk	Not clear as to whether groups were similar at baseline

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Anonymous 1976	Treatment of lepromatous leprosy, not of ENL
Arruda 1986	Treatment of lepromatous leprosy, not of ENL
Browne 1981	No RCT
Dawlah 2002	No RCT
de Almeida Neto 1981	No separate results for ENL
de Carsalade 2003	No RCT

(Continued)

Garbino 2006	No specific treatment of ENL, but treatment of ulnar neuropathy in participants with type 1 and type 2 reactions
Hastings 1970	No RCT
Huang 1987	No RCT
Imkamp 1968	No RCT
Imkamp 1973	No RCT
Jamet 1992	Treatment of lepromatous leprosy, not of ENL
Kar 1988	Randomisation by alternation
Karat 1971a	Treatment of lepromatous leprosy, not of ENL
Karat 1971b	Prophylaxis treatment, not treatment of ENL
Levy 1973	No RCT
Manungo 1982a	Treatment of lepromatous leprosy, not of ENL
Manungo 1982b	No RCT
Moreira 1998	No RCT
Partida-Sanchez 1998	No RCT
Penna 2005	Only methodology and intake results were described, trial not completed
Pettit 1967	No RCT
Plock 1976	No RCT
Ramu 1979	Randomisation by alternation
Rodriguez 1974	Treatment of lepromatous and borderline leprosy, not of ENL
Sharma 1982	No RCT
Sharma 1986	No RCT
Sheskin 1969a	No RCT
Sheskin 1971	No RCT
Sheskin 1983	No RCT

(Continued)

Sunderkotter 2005	No RCT
Vides 1999	No RCT
Zaheer 1993	Treatment of multibacillary (MB) leprosy, not of ENL
Zhang 2008	No RCT

Characteristics of ongoing studies [ordered by study ID]

Salim 2009

Trial name or title	Montelukast in ENL Reaction
Methods	design: parallel groups randomised controlled trial single blind
Participants	<ul style="list-style-type: none">• MB leprosy• ENL reaction• age 15 to 65• weight > 35kg• patient willing to participate, including agreeing to investigations and admission• adequate past records• no steroid received in past 4 weeks
Interventions	1) prednisolone alone 2) prednisolone plus montelukast 3) montelukast alone Prednisolone starting at 40 mg daily tapered over 12 weeks. Montelukast 10 mg for 16 weeks
Outcomes	<ul style="list-style-type: none">• absence of new nerve function impairment• decrease in ENL score• incidence of adverse effects Timing of outcome assessment at 24 weeks
Starting date	December 2006
Contact information	Abdul H Salim, MBBS: dfsalim@citechco.net
Notes	

DATA AND ANALYSES

Comparison 1. Thalidomide versus aspirin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission of skin lesions	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 2. 100 mg thalidomide versus 300 mg thalidomide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission of skin lesions	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Change in ENL severity (proportion improved)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Time to next clinical ENL episode	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 3. Pentoxifylline versus thalidomide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission of skin lesions	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 4. Clofazimine versus prednisolone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission of skin lesions	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Time to next clinical ENL episode	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 5. Clofazimine versus thalidomide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to next clinical ENL episode	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 6. Indomethacin versus prednisolone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission of skin lesions	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Change in ENL severity (proportion improved)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Time to next clinical ENL episode	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 7. Indomethacin versus chloroquine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in ENL severity (proportion improved)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Time to next clinical ENL episode	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 8. Indomethacin versus aspirin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in ENL severity (proportion improved)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Time to next clinical ENL episode	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 9. Levamisole versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in ENL severity (proportion improved)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Thalidomide versus aspirin, Outcome 1 Remission of skin lesions.

Review: Interventions for erythema nodosum leprosum

Comparison: 1 Thalidomide versus aspirin

Outcome: 1 Remission of skin lesions

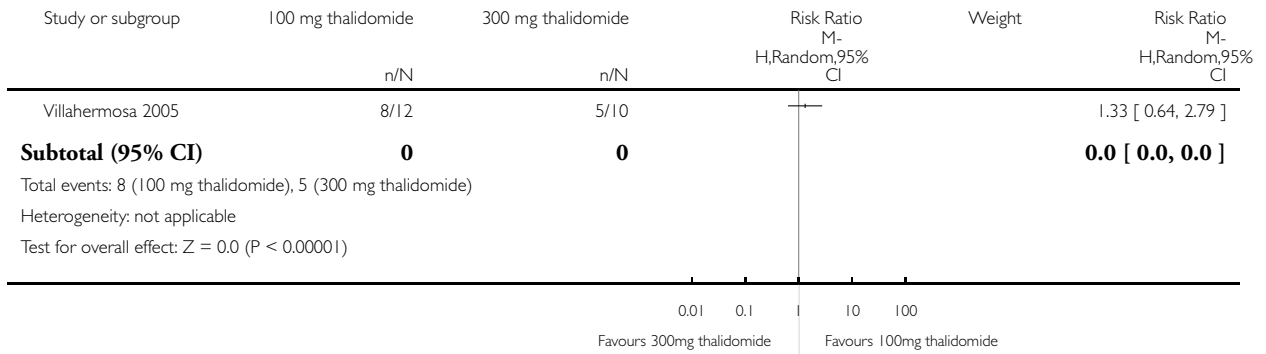
Study or subgroup	thalidomide	aspirin	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
	n/N	n/N			
Iyer 1971	26/50	9/42			2.43 [1.28, 4.59]
Subtotal (95% CI)	0	0			0.0 [0.0, 0.0]
Total events: 26 (thalidomide), 9 (aspirin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					
			0.01 0.1 10 100		
			Favours aspirin	Favours thalidomide	

Analysis 2.1. Comparison 2 100 mg thalidomide versus 300 mg thalidomide, Outcome 1 Remission of skin lesions.

Review: Interventions for erythema nodosum leprosum

Comparison: 2 100 mg thalidomide versus 300 mg thalidomide

Outcome: 1 Remission of skin lesions

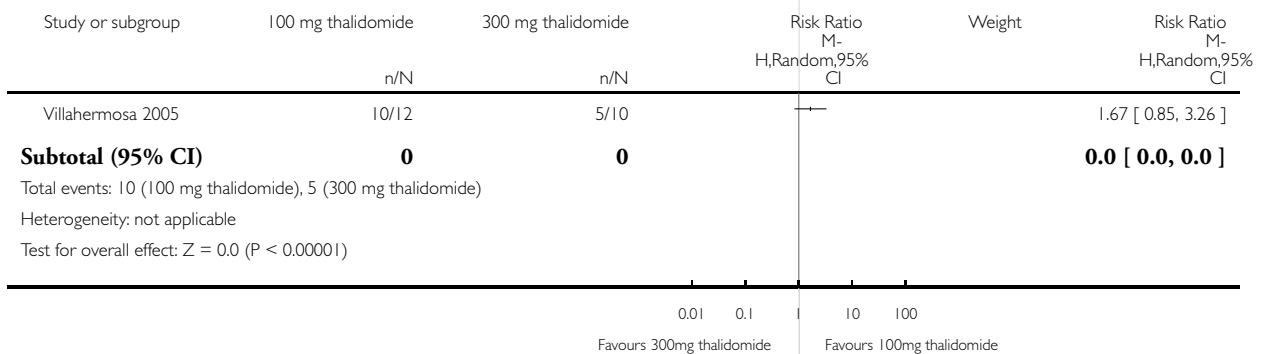


Analysis 2.2. Comparison 2 100 mg thalidomide versus 300 mg thalidomide, Outcome 2 Change in ENL severity (proportion improved).

Review: Interventions for erythema nodosum leprosum

Comparison: 2 100 mg thalidomide versus 300 mg thalidomide

Outcome: 2 Change in ENL severity (proportion improved)

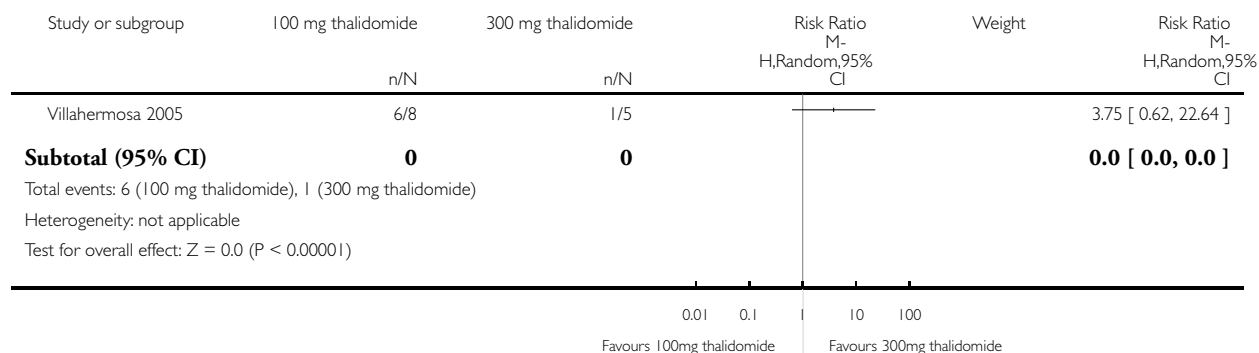


Analysis 2.3. Comparison 2 100 mg thalidomide versus 300 mg thalidomide, Outcome 3 Time to next clinical ENL episode.

Review: Interventions for erythema nodosum leprosum

Comparison: 2 100 mg thalidomide versus 300 mg thalidomide

Outcome: 3 Time to next clinical ENL episode

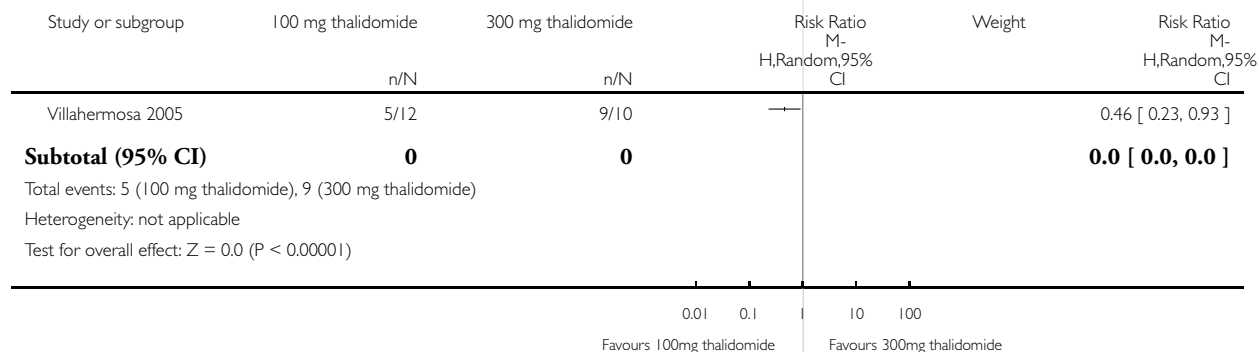


Analysis 2.4. Comparison 2 100 mg thalidomide versus 300 mg thalidomide, Outcome 4 Adverse effects.

Review: Interventions for erythema nodosum leprosum

Comparison: 2 100 mg thalidomide versus 300 mg thalidomide

Outcome: 4 Adverse effects

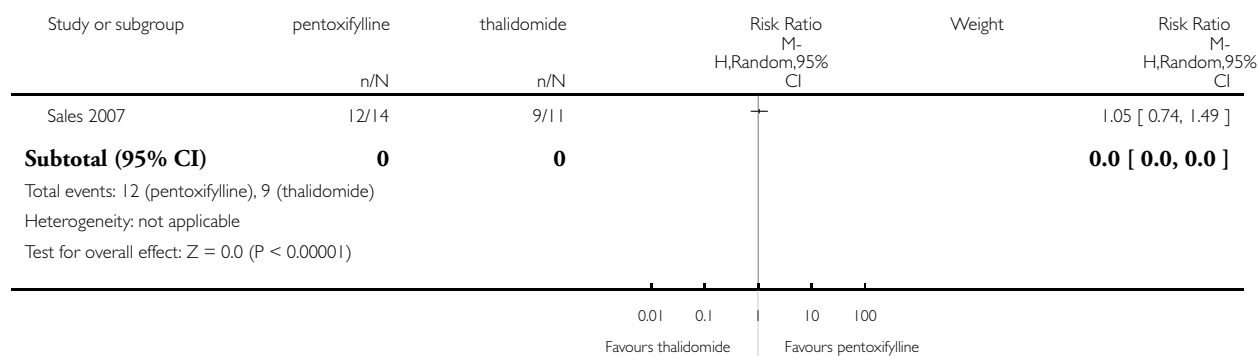


Analysis 3.1. Comparison 3 Pentoxifylline versus thalidomide, Outcome 1 Remission of skin lesions.

Review: Interventions for erythema nodosum leprosum

Comparison: 3 Pentoxifylline versus thalidomide

Outcome: 1 Remission of skin lesions

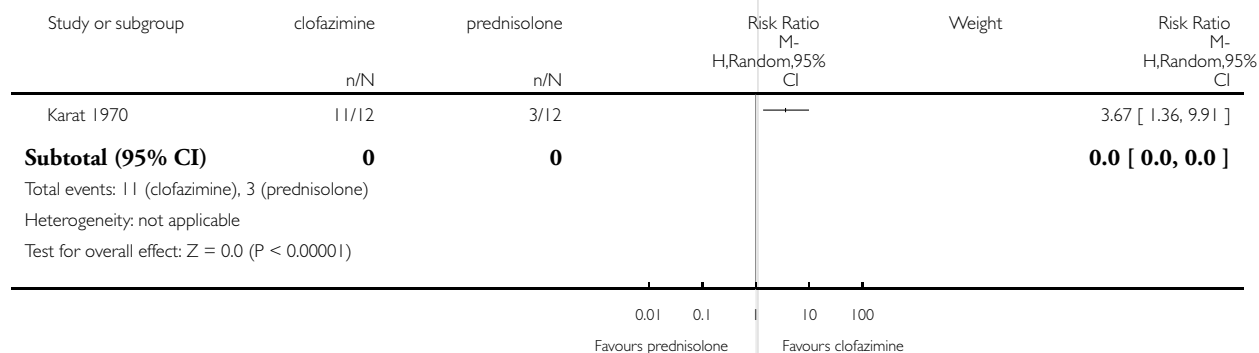


Analysis 4.1. Comparison 4 Clofazimine versus prednisolone, Outcome 1 Remission of skin lesions.

Review: Interventions for erythema nodosum leprosum

Comparison: 4 Clofazimine versus prednisolone

Outcome: 1 Remission of skin lesions

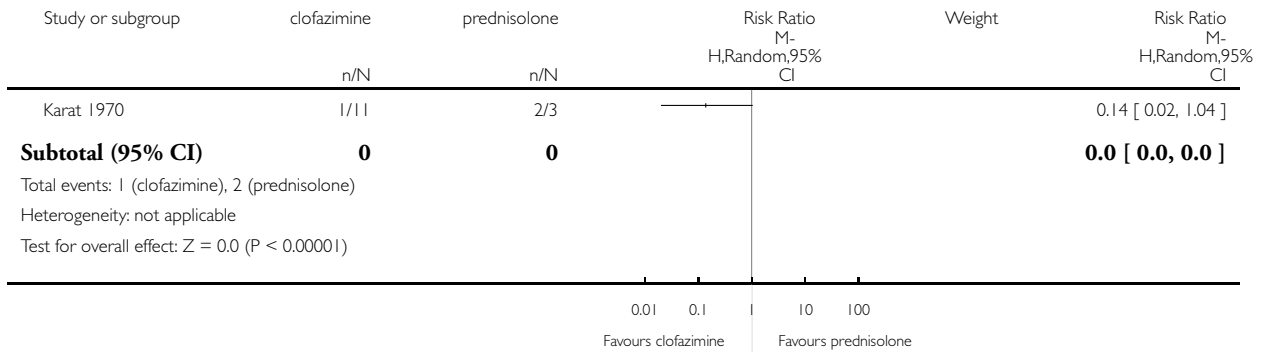


Analysis 4.2. Comparison 4 Clofazimine versus prednisolone, Outcome 2 Time to next clinical ENL episode.

Review: Interventions for erythema nodosum leprosum

Comparison: 4 Clofazimine versus prednisolone

Outcome: 2 Time to next clinical ENL episode

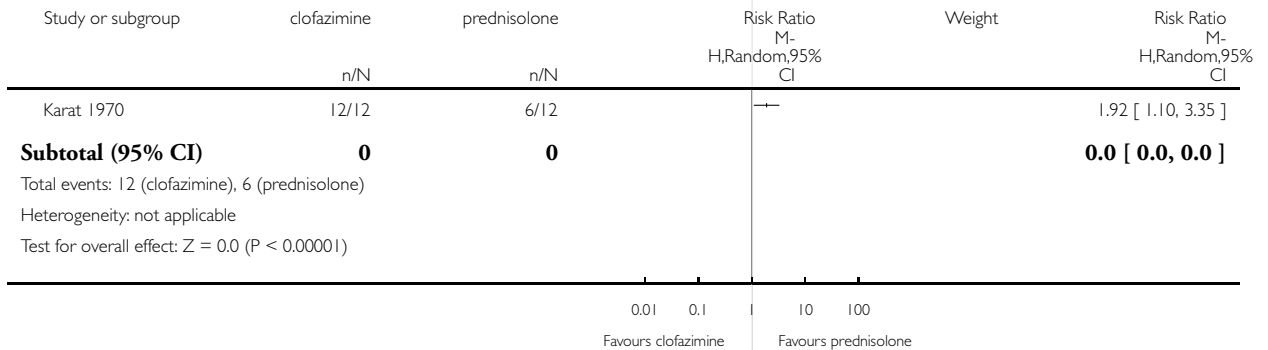


Analysis 4.3. Comparison 4 Clofazimine versus prednisolone, Outcome 3 Adverse effects.

Review: Interventions for erythema nodosum leprosum

Comparison: 4 Clofazimine versus prednisolone

Outcome: 3 Adverse effects

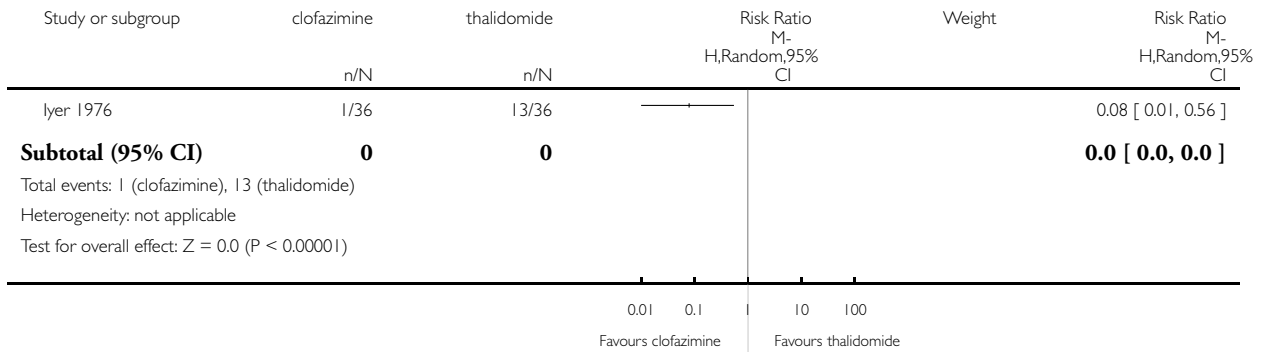


Analysis 5.1. Comparison 5 Clofazimine versus thalidomide, Outcome 1 Time to next clinical ENL episode.

Review: Interventions for erythema nodosum leprosum

Comparison: 5 Clofazimine versus thalidomide

Outcome: 1 Time to next clinical ENL episode

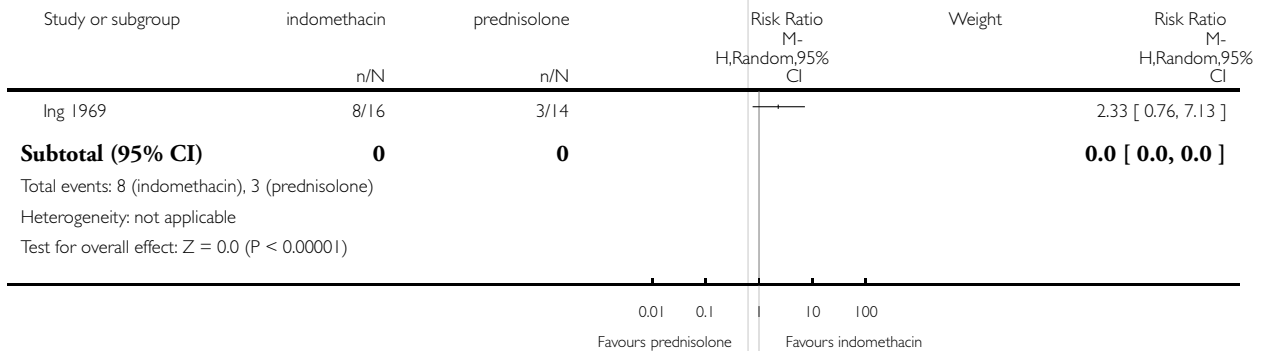


Analysis 6.1. Comparison 6 Indomethacin versus prednisolone, Outcome 1 Remission of skin lesions.

Review: Interventions for erythema nodosum leprosum

Comparison: 6 Indomethacin versus prednisolone

Outcome: 1 Remission of skin lesions

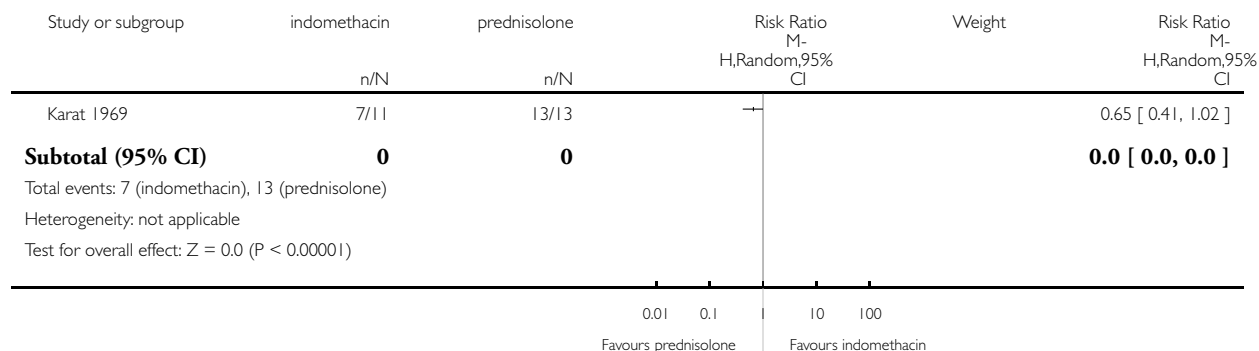


Analysis 6.2. Comparison 6 Indomethacin versus prednisolone, Outcome 2 Change in ENL severity (proportion improved).

Review: Interventions for erythema nodosum leprosum

Comparison: 6 Indomethacin versus prednisolone

Outcome: 2 Change in ENL severity (proportion improved)

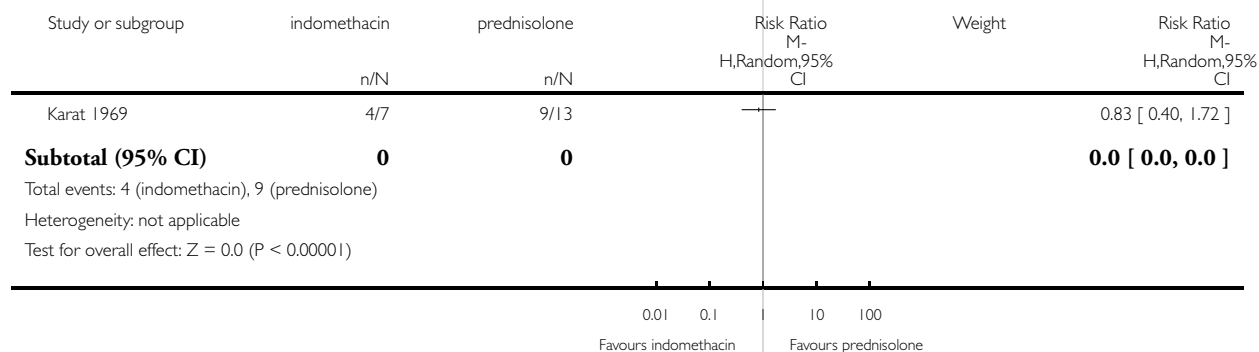


Analysis 6.3. Comparison 6 Indomethacin versus prednisolone, Outcome 3 Time to next clinical ENL episode.

Review: Interventions for erythema nodosum leprosum

Comparison: 6 Indomethacin versus prednisolone

Outcome: 3 Time to next clinical ENL episode

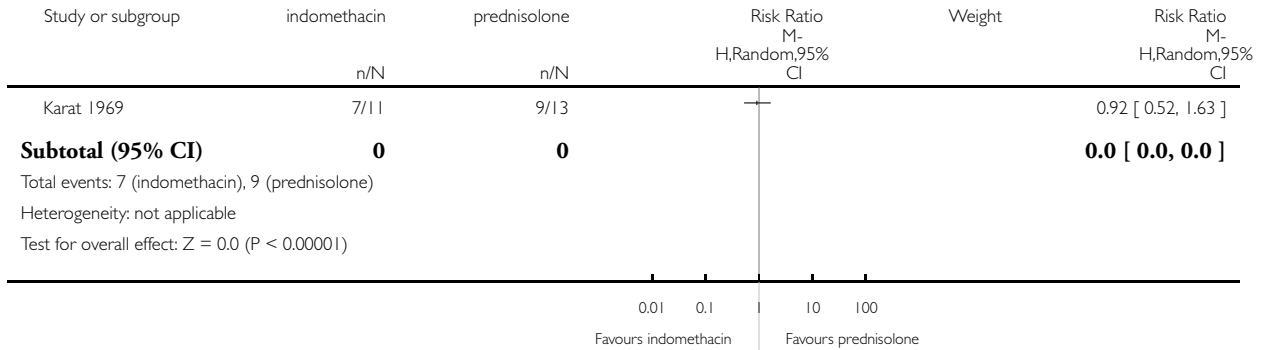


Analysis 6.4. Comparison 6 Indomethacin versus prednisolone, Outcome 4 Adverse effects.

Review: Interventions for erythema nodosum leprosum

Comparison: 6 Indomethacin versus prednisolone

Outcome: 4 Adverse effects

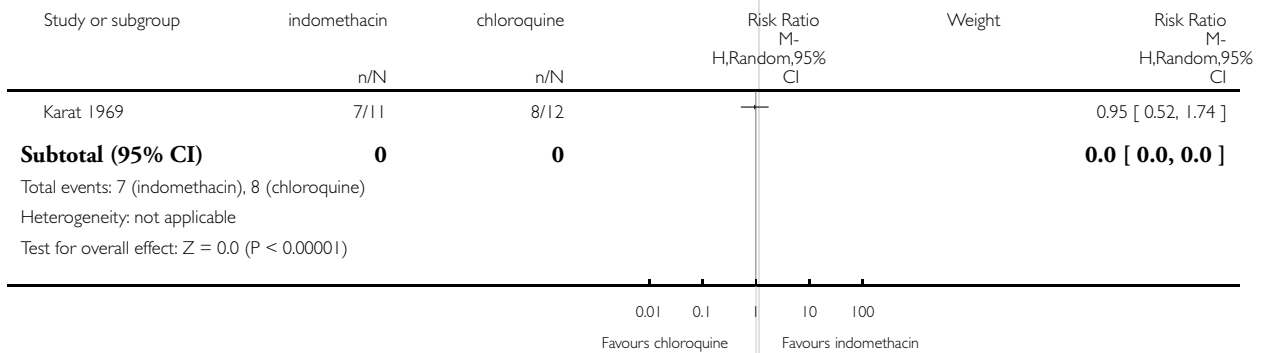


Analysis 7.1. Comparison 7 Indomethacin versus chloroquine, Outcome 1 Change in ENL severity (proportion improved).

Review: Interventions for erythema nodosum leprosum

Comparison: 7 Indomethacin versus chloroquine

Outcome: 1 Change in ENL severity (proportion improved)

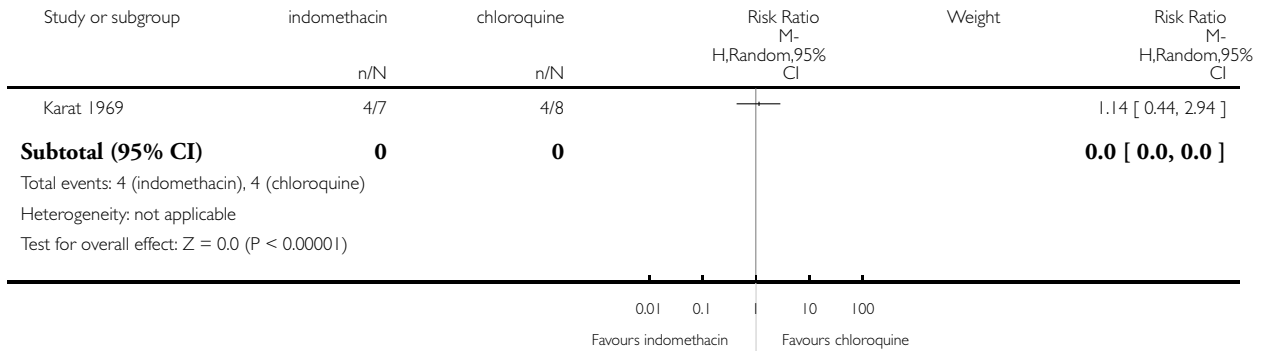


Analysis 7.2. Comparison 7 Indomethacin versus chloroquine, Outcome 2 Time to next clinical ENL episode.

Review: Interventions for erythema nodosum leprosum

Comparison: 7 Indomethacin versus chloroquine

Outcome: 2 Time to next clinical ENL episode

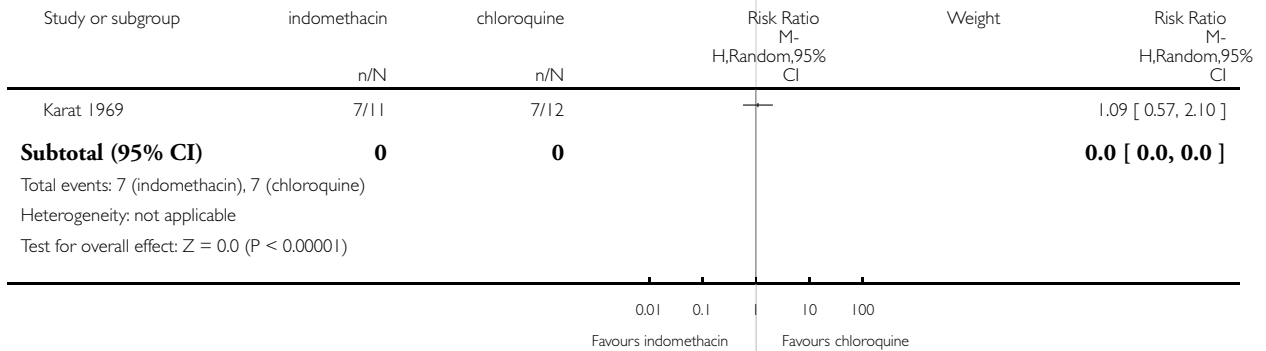


Analysis 7.3. Comparison 7 Indomethacin versus chloroquine, Outcome 3 Adverse effects.

Review: Interventions for erythema nodosum leprosum

Comparison: 7 Indomethacin versus chloroquine

Outcome: 3 Adverse effects

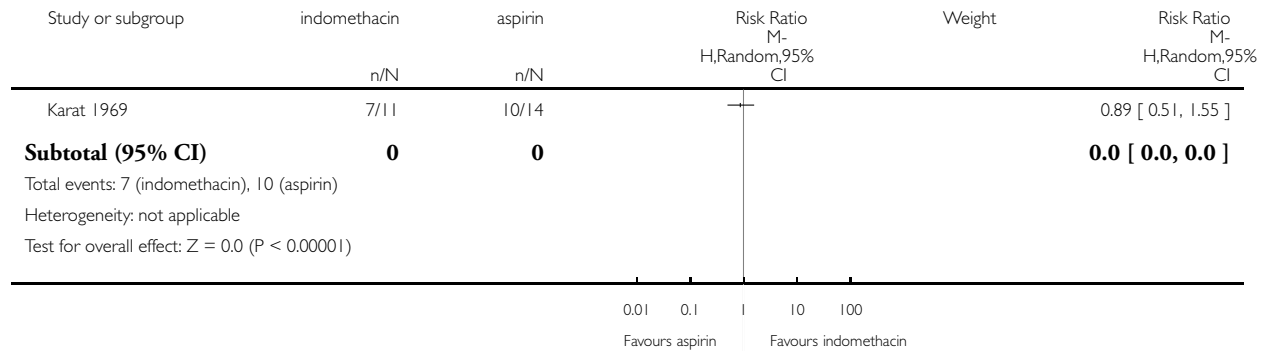


Analysis 8.1. Comparison 8 Indomethacin versus aspirin, Outcome 1 Change in ENL severity (proportion improved).

Review: Interventions for erythema nodosum leprosum

Comparison: 8 Indomethacin versus aspirin

Outcome: 1 Change in ENL severity (proportion improved)

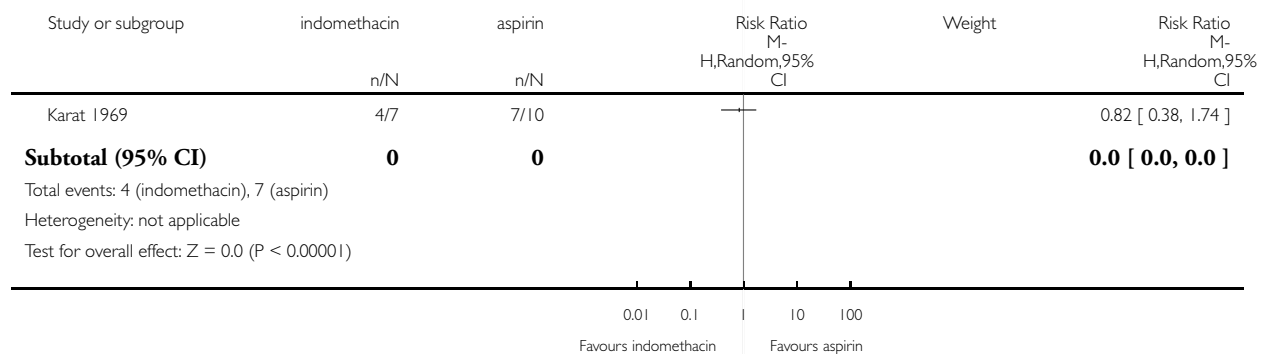


Analysis 8.2. Comparison 8 Indomethacin versus aspirin, Outcome 2 Time to next clinical ENL episode.

Review: Interventions for erythema nodosum leprosum

Comparison: 8 Indomethacin versus aspirin

Outcome: 2 Time to next clinical ENL episode

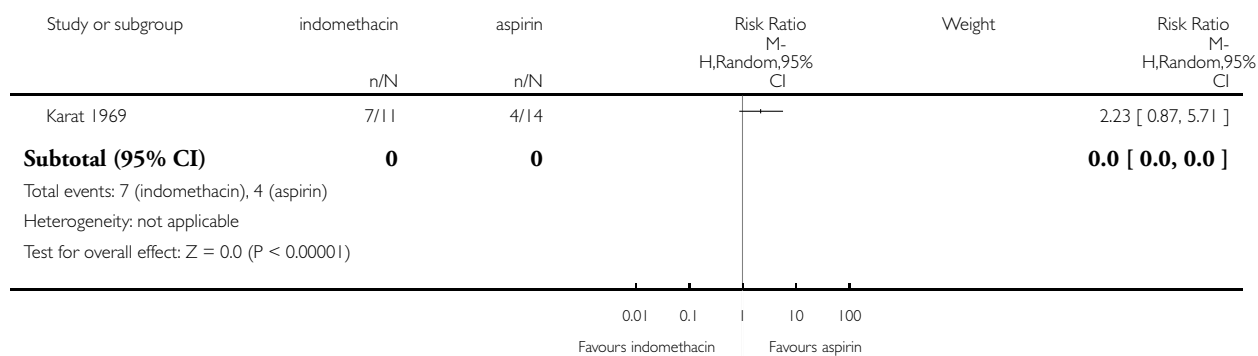


Analysis 8.3. Comparison 8 Indomethacin versus aspirin, Outcome 3 Adverse effects.

Review: Interventions for erythema nodosum leprosum

Comparison: 8 Indomethacin versus aspirin

Outcome: 3 Adverse effects

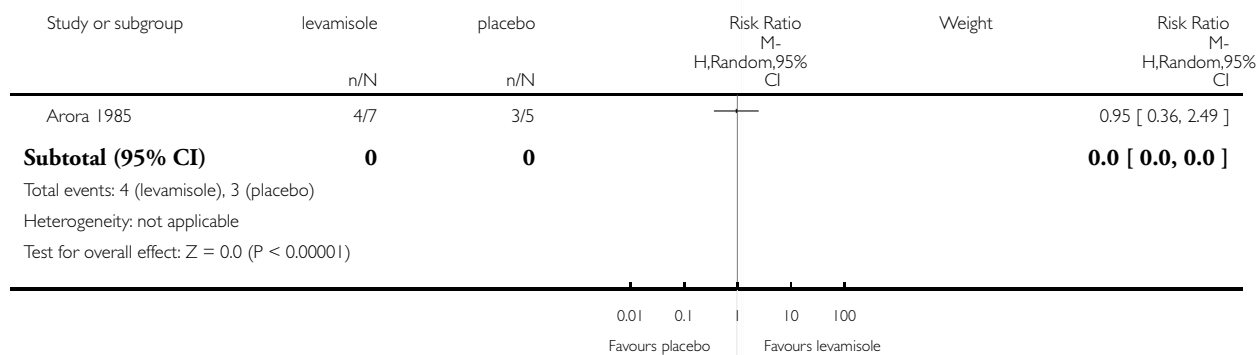


Analysis 9.1. Comparison 9 Levamisole versus placebo, Outcome 1 Change in ENL severity (proportion improved).

Review: Interventions for erythema nodosum leprosum

Comparison: 9 Levamisole versus placebo

Outcome: 1 Change in ENL severity (proportion improved)



APPENDICES

Appendix 1. Cochrane Library search strategy

#1(type 2 leprosy):ti,ab,kw or (lepr* reaction):ti,ab,kw or (erythema nodosum) or (erythema nodosum leprosum) or 'ENL':ti,ab,kw or (borderline leprosy):ti,ab,kw or (lepromatous leprosy):ti,ab,kw
#2MeSH descriptor Leprosy, Borderline, this term only
#3MeSH descriptor Leprosy, Lepromatous, this term only
#4(SR-SKIN)
#5(#1 OR #2 OR #3)
#6(#5 AND NOT #4)

Appendix 2. MEDLINE search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. humans.sh.
10. 8 and 9
11. leprosy.mp. or exp LEPROSY/
12. type 2 reaction.mp.
13. lepra reaction.mp.
14. ENL.mp.
15. *Erythema Nodosum/
16. LEPROSY, BORDERLINE/
17. LEPROSY, LEPRMATOUS/
18. 11 and 12
19. 11 and 14
20. 15 or 16 or 17 or 18 or 19
21. 10 and 20

Appendix 3. EMBASE search strategy

1. random\$.mp.
2. factorial\$.mp.
3. crossover\$.mp.
4. placebo\$.mp. or PLACEBO/
5. (doubl\$ adj blind\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl\$ adj blind\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. assign\$.mp.
8. volunteer\$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/

13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. leprosy.mp. or exp LEPROSY/
15. type 2 reaction.mp.
16. 14 and 15
17. lepra reaction.mp.
18. erythema nodosum leprosum.mp. or exp Erythema Nodosum Leprosum/
19. ENL.mp.
20. borderline leprosy.mp. or exp Borderline Leprosy/
21. lepromatous leprosy.mp. or exp Lepromatous Leprosy/
22. 16 or 17 or 18 or 19 or 20 or 21
23. 13 and 22

Appendix 4. AMED search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. humans.sh.
10. 8 and 9
11. leprosy.mp. or exp LEPROSY/
12. type 2 reaction.mp.
13. 11 or 12
14. 10 and 13

Appendix 5. LILACS search strategy

((Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control\$ or tw aleat\$ or tw random\$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic\$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Palavras] and ((eritema nodoso leproso) or lepra or (leporreacion) [Palavras] or lepra lepromatosa) or (lepra bipolar) or (lepra dimorfa intermedia) [Palavras]

Appendix 6. CINAHL search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. humans.sh.
10. 8 and 9

- 11. leprosy.tx.
- 12. type 2 reaction.tx.
- 13. erythema nodosum leprosum.tx.
- 14. 11 and 12
- 15. 11 and 13
- 16. 14 or 15
- 9. 10 and 16.

WHAT'S NEW

Last assessed as up-to-date: 11 March 2009.

Date	Event	Description
12 September 2012	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 3, 2009

Date	Event	Description
6 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Link with editorial base and co-ordinate contributions from co-authors (NvV)

Draft protocol (NvV, DL, WvB, JRJ, JHR)

Run search (NvV, FD)

Identify relevant titles and abstracts from searches (NvV, JHR)

Obtain copies of trials (NvV)

Selection of trials (NvV, JHR)

Extract data from trials (NvV)

Enter data into RevMan (NvV) Check data (JHR)

Carry out analysis (NvV, JHR)

Interpret data (NvV, DL, WvB, JHR)

Draft final review (NvV, DL, WvB, JRJ, JHR)

Update review (NvV)

Guarantor review (NvV)

DECLARATIONS OF INTEREST

DNL has been a paid advisor to the drug company Pharmion (who makes thalidomide) advising them on their application to have thalidomide registered within the EU.

SOURCES OF SUPPORT

Internal sources

- The Netherlands Leprosy Relief, Netherlands.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the original published protocol outcomes recorded for four weeks or less from the start of treatment were considered to reflect short-term benefit, and data that were recorded for three months or longer from the start of treatment were considered long-term outcomes. After extracting data, we found that timing of outcome assessment varied between four days and one year from the start of treatment.

We decided that studies with outcomes of four weeks or less from the start of treatment were considered as short-term outcomes. We added medium-term outcomes defined as outcomes between four weeks and six months from the start of treatment and changed long-term outcome assessment to more than six months from the start of treatment.

In the original published protocol we planned for two authors to independently extract the data, but it was more efficient to have one author extract the data and enter it into Review Manager, and a second author to check the data.

INDEX TERMS

Medical Subject Headings (MeSH)

Aspirin [therapeutic use]; Clofazimine [therapeutic use]; Erythema Nodosum [*drug therapy]; Leprostatic Agents [*therapeutic use]; Leprosy, Lepromatous [*drug therapy]; Prednisolone [therapeutic use]; Randomized Controlled Trials as Topic; Remission Induction; Thalidomide [therapeutic use]

MeSH check words

Humans