# Interventions for Old World cutaneous leishmaniasis (Review)

González U, Pinart M, Reveiz L, Alvar J


This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

http://www.thecochranelibrary.com

## TABLE OF CONTENTS

**[Intervention Review]**

# Interventions for Old World cutaneous leishmaniasis

Urbà González [1], Mariona Pinart[1], Ludovic Reveiz[2], Jorge Alvar[3]

[1]Department of Dermatology, Research Unit for Evidence-based Dermatology, Hospital Plató, Barcelona, Spain. [2]Research Institute - School Of Medicine, Fundación Universitaria Sánitas , Bogotá, Colombia. [3]Control of Neglected Tropical Diseases (WHO/CDS/NTD/IDM), World Health Organization, Geneva 27, Switzerland

Contact address: Urbà González , Department of Dermatology, Research Unit for Evidence-based Dermatology, Hospital Plató, c/ Plato 21, Barcelona, Catalunya, 08006, Spain. urba.gonzalez@hospitalplato.com . (Editorial group: Cochrane Skin Group.)

*Cochrane Database of Systematic Reviews*, Issue 1, 2009 (Status in this issue: *Unchanged*)

DOI: 10.1002/14651858.CD005067.pub3
**This version first published online:** 8 October 2008 in Issue 4, 2008.
**Last assessed as up-to-date:** 30 March 2008. (Help document - Dates and Statuses explained)

**This record should be cited as:** González U, Pinart M, Reveiz L, Alvar J. Interventions for Old World cutaneous leishmaniasis. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD005067. DOI: 10.1002/14651858.CD005067.pub3.

## ABSTRACT

### Background

Cutaneous leishmaniasis is caused by a parasitic infection and is considered one of the most serious skin diseases in many developing countries. Antimonials are the most commonly prescribed treatment but other drugs have been used with varying success.

### Objectives

To assess the effects of treatments for Old World cutaneous leishmaniasis (OWCL).

### Search strategy

We searched the Cochrane Skin Group Specialised Register (April 2008), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 2, 2008), MEDLINE (2003-April 2008), EMBASE (2005-April 2008), CINAHL (1982-August 2007), LILACS (from inception to April 2008) and ongoing trials databases (August 2007).

### Selection criteria

Randomised controlled trials assessing treatments in immuno-competent people with OWCL confirmed by smear, histology, culture or polymerase chain reaction.

### Data collection and analysis

Two authors independently assessed trial quality and extracted data.

### Main results

We included 49 trials involving 5559 participants. Reporting quality was generally poor and only two studies contained sufficiently similar data to pool.

In *Leishmania major* infections, there was good RCT evidence of benefit of cure around 3 months after treatment when compared to placebo for 200 mg oral fluconazole (1 RCT n = 200, RR 2.78; 95% CI 1.86, 4.16), topical 15% paromomycin + 12% methylbenzethonium chloride (PR-MBCL) (1 RCT n = 60, RR 3.09; 95% CI 1.14, 8.37) and photodynamic therapy (1 RCT n = 60, RR 7.02; 95% CI 3.80, 17.55). Topical PR-MBCL was less efficacious than photodynamic therapy (1 RCT n = 65, RR 0.44; 95% CI 0.29,

0.66). Oral pentoxifylline was a good adjuvant therapy to intramuscular meglumine antimoniate (IMMA) when compared to IMMA plus placebo (1 RCT n = 64, RR 1.63; 95% CI 1.11, 2.39)

In *Leishmania tropica* infections, there was good evidence of benefit for the use of 200 mg oral itraconazole for 6 weeks compared with placebo (1 RCT n = 20, RR 7.00; 95% CI 1.04, 46.95), for intralesional sodium stibogluconate (1 RCT n = 292, RR 2.62; 95% CI 1.78, 3.86), and for thermotherapy compared with intramuscular sodium stibogluconate (1 RCT n = 283, RR 2.99; 95% CI 2.04, 4.37).

**Authors' conclusions**

Most trials have been designed and reported poorly, resulting in a lack of evidence for potentially beneficial treatments. There is a desperate need for large well conducted studies that evaluate long-term effects of current therapies. We suggest the creation of an international platform to improve quality and standardization of future trials in order to inform clinical practice.

## PLAIN LANGUAGE SUMMARY

**Interventions for Old World cutaneous leishmaniasis**

Old World cutaneous leishmaniasis (OWCL) is a disfiguring and stigmatising disease occuring in areas of the Mediterranean, Middle East and Asia, caused by a parasitic infection transmitted by sandflies. Pentavalent antimonial drugs such as sodium stibogluconate (Pentostam, Stibanate) and meglumine antimoniate (Glucantime), have been used since the 1940s as the main first-line therapeutic agents for cutaneous leishmaniasis worldwide. However, many different treatments for OWCL have been described.

We assessed 49 trials involving different interventions. In *Leishmania major* infections there was good evidence of benefit for the use of 200 mg oral fluconazole for 6 weeks, topical paromomycin + 12% methylbenzethonium chloride (MBCL), photodynamic therapy and oral pentoxifylline as an adjuvant therapy to intramuscular meglumine antimoniate. However, compared with other interventions there was not enough good evidence for the use of intralesional zinc sulphate weekly compared with antimonials, and topical 15% paromomycin +12% MBCL for 28 days compared with photodynamic therapy. There was good trial evidence of benefit for the use of 200 mg oral itraconazole for 6 weeks in *Leishmania tropica* infections, and to support the use of intralesional sodium stibogluconate and thermotherapy rather than intramuscular stibogluconate. There was good RCT evidence for not supporting the use of topical 5% imiquimod cream combined with antimonials.

The major drawback associated with intralesional treatments is local pain which causes significant patient discomfort. Intramuscular or intravenous drugs are associated with more severe adverse effects. While there is no general consensus on optimal treatment, alternatives to intramuscular or intravenous treatments are under active investigation. Efficacious, well tolerated and inexpensive oral agents are clearly needed in OWCL because we still do not have an ideal treatment that can treat all target species with few serious adverse effects.

The current evidence for the treatment of OWCL has many limitations and there is much scope for improving the design and reporting of clinical trials. None of the studies reported the degree of functional and aesthetic impairment and only two assessed the quality of life. Since resources are limited for clinical research into neglected diseases there is a need to prioritise and carry out properly designed clinical trials.

We suggest the creation of an international platform to improve the quality and standardization of future trials in order to develop a better evidence-based approach.

# BACKGROUND

## Description of the condition

### Definition and epidemiology

The leishmaniases are a group of diseases caused by infection with protozoan parasites of the genus *Leishmania*. The infection is transmitted by bites from sandflies infected with the parasite (Desjeux 1996).

Leishmaniasis has two main clinical presentation forms (cutaneous and visceral), which are associated with a broad range of signs, symptoms and degrees of severity (Herwaldt 1999; Reithinger 2007).

#### Cutaneous leishmaniasis

Cutaneous leishmaniasis (CL) is a worldwide public health and a social problem in many developing countries. It can affect the skin and mucous membranes, and is caused by different *Leishmania* species widespread in 88 countries in the New and Old World. Old World cutaneous leishmaniasis (OWCL) is present in many endemic areas in North Africa, the Mediterranean, the Middle East, the Indian subcontinent and Central Asia. The species responsible for OWCL are mainly *L. major* and *L. tropica. Leishmania infantum* and *L. donovani* can also cause localised CL but are observed less frequently in the Mediterranean areas. Diffuse CL is uncommon and is caused by *L. aethiopica* in Africa (Alrajhi 2003; Reithinger 2007). With regard to transmission, OWCL is divided into two main groups:

- Zoonotic cutaneous leishmaniasis (ZCL), where the parasite is transmitted from a range of animals to humans. It is seen in rural areas and is geographically distributed in the Middle East, Northwestern China and North Africa. ZCL is mostly caused by *L. major* and often heals spontaneously in about two to four months, although in some cases it may persist for as long as five years;
- Anthroponotic cutaneous leishmaniasis (ACL), where the parasite is transmitted from person to person. It is an urban disease and is geographically distributed in the Middle East, the Indian Subcontinent, and Western Asia. ACL is mostly caused by *L. tropica.* Lesions may persist for 6 to 15 months before healing with significant scarring.

CL has been also categorised into four different clinical forms:

**Localised**

In the localised form the parasite is confined to the skin. After an incubation period of 1 to 12 weeks a papule or bump develops at the site of the insect bite. The papule grows and turns into an ulcer. A typical lesion of the localised form of CL is a painless papule or ulcer covered with an adherent crust of dried exudate. Most people with CL have 1 or 2 lesions varying in size from 0.5 to 3 cm in diameter, usually on exposed parts of the body such as the face, arms or legs. There is, however, considerable variation: people may have as many as 200 simple skin lesions; some lesions grow but do not ulcerate (nodules); and some *Leishmania* species also infect the lymphatic system producing lesions along the lymphatic channels (nodular lymphangitis). Secondary bacterial infection is common, causing pain and serious disability. Most lesions heal spontaneously over months or years, leaving permanent scarring with skin thinning. Scarring of leishmaniasis is typical with a depigmented centre and a pigmented border (Reithinger 2007).

**Recidivans**

This form appears in around 5% of the participants suffering CL by *L. tropica* and is characterised by microsatellite and confluent lesions that relapse and finally ulcerate in the border of previous scars.

**Diffuse leishmaniasis**

Diffuse leishmaniasis affects only the skin but with generalised skin lesions. It is seen mainly in Africa transmitted by *L. aethiopica* (Alrajhi 2003). Post kala-azar dermal leishmaniasis is a is a form of diffuse cutaneous leishmaniasis and a sequel of visceral leishmaniaisis that may appear in affected individuals up to 20 years after the being partially treated, untreated or in those considered adequately treated (Rathi 2005).

**Mucosal leishmaniasis**

In mucosal leishmaniasis the parasite may spread to the mucous membranes, especially those of the nose, mouth and throat, and cause extensive damage and disfiguration. It is seen mainly in South America but it can also be caused by species from Old World countries including *L. tropica*, *L. major* and *L. infantum*.

#### Visceral leishmaniasis or kala-azar

This form of leishmaniasis is caused by *L. donovani* in Sudan and East Africa, or *L. infantum* and may present as an opportunistic infection in people with a defect in the immunological defences, such as those with HIV infection (Alvar 2008). The parasite affects internal organs, in particular the spleen, liver, bone marrow and lymph nodes. It is potentially a deadly disease if left untreated.

### Causes and impact

In many tropical and subtropical developing countries protozoan parasites are amongst the most common infectious agents and have serious consequences for socio-economic development (WHO 2002; Alvar 2006). The World Health Organisation (WHO) considers leishmaniasis to be one of the most serious parasitic diseases and the World Health Assembly has advocated a concertation for its control (WHO 2007). The overall prevalence is 12 million with an estimated 1.5 million new cases of CL per year. Approximately 350 million people, who are often impoverished, are at risk of contracting the disease (WHO 2001; Alvar 2006). Currently, the disease appears to be underestimated and on the rise in several countries.

OWCL is also increasingly seen in immigrants, military personnel, humanitarian aid workers, tourists and travellers from endemic areas. However, imported cutaneous leishmaniasis is still missed by most Western physicians. Suspected skin lesions need to be analysed with biopsies and tissue smears in order to make an accurate diagnosis. (Reithinger 2007).

### Diagnosis

Clinically diagnosed OWCL should be confirmed using the traditional diagnostic techniques of smear, parasite culture and histological analysis of skin biopsies. Circulating antibodies in the bloodstream are in general low or undetectable in cases of OWCL. Modern molecular diagnostic techniques, mainly the polymerase chain reaction test (PCR), appear to be the most sensitive single diagnostic test for species identification in skin samples (Schalling 2002; Faber 2003).

## Description of the intervention

Issues of treatment in CL are difficult to deal with because there are many factors that can influence the efficacy of drugs: size, number and appearance of the lesions, the duration of the disease prior to treatment, frequency and time to self-healing, frequency of relapse and re-infection, frequency and severity of either mucosal or diffuse involvement, immunosuppression, co-infections and prior anti-*Leishmania* treatment. The location of the lesion (e.g. face or joints), age of the patient (e.g. adults or children) and gender are also factors that often determine the choice of treatment. Other factors are intrinsic and related to the different *Leishmania* species. An effective treatment in one geographical area for a given organism may not work in a different geographical area or for a different organism in the same location. In these cases, efficacy depends not only on the *Leishmania* species but also on the response of the person to the parasite and factors such as immunity, variable clinical response to treatments, drug toxicity, drug resistance, HIV co-infection and compliance.

Many different treatments for OWCL have been described ( Modabber 2007; WHO 2008, in press). Nonetheless, several authors have pointed out the lack of properly controlled clinical trials (Hepburn 2001;Herwaldt 1999; Moskowitz 1999). Another disadvantage and paradox is the lack of availability of most of these drugs in rural and poorer areas where the majority of leishmaniasis are encountered.

### Systemic Treatments

Systemic treatments are generally given to those with CL who present with big, multiple or disseminated lesions and in those who have simple lesions involving cosmetically sensitive areas or joints, or with the presence of nodular lymphangitis. The current mainstays of systemic treatment for OWCL are the pentavalent antimony compounds (sodium stibogluconate (Pentostam, Stibanate, SSG) and meglumine antimoniate (MA)). They cannot be administered orally. The recommended dosage is 20 mg/kg/day of SSG intramuscularly or intravenously for 20 days or 60 mg/kg/day of MA (Glucantime) (Momeni 2002). They have also been used frequently as a control for studies of new treatments. However, there are concerns about their cost, toxicity and the development of drug resistance. Parenteral antimonial drugs are associated with severe adverse effects, including nausea, vomiting, diarrhoea, skin eruptions, dizziness, cardiac arrhythmia, hypotension, arthralgia, myalgia, abdominal discomfort, headache and reversible elevation of hepatocellular enzymes, occasional anaemia and thrombocytopenia which are often dose-dependent. Pain at the site of the injection was greater when administered IL than IV/IM (Iraji 2005; Momeni 2002; Salmanpour 2006). Whilst there is no general consensus on optimum treatment, alternatives to systemic antimonials are under active investigation. Combination therapies may also help to reduce drug resistance.

Azole antifungal drugs are potential therapeutic agents in CL available for oral administration. The firsts reports of oral ketoconazole for the treatment of CL in both the New and the Old World came out in the early 1980s (Urcuyo 1982; Weinrauch 1983a; Weinrauch 1983b). However, reports of liver toxicity made it necessary to search for other azoles. In the late 1980s another azole called itraconazole was touted as a treatment for CL (Cauwenberg 1986; Borelli 1987). Recently, fluconazole, another antifungal azole (Alrajhi 2002), has been used as an alternative therapy for CL.

The antibiotic/antileprosy drug dapsone has been proposed as an inexpensive, oral alternative to the treatment currently used for CL (Dogra 1986; Dogra 1990) but the main side effect of dapsone is blood cell destruction and anaemia. Allopurinol (a medicine used to treat gout) alters protein synthesis and inhibits the growth of *Leishmania in vitro* (Momeni 2002) and has been suggested as a potential therapeutic agent for the treatment of both cutaneous and visceral leishmaniasis (VL) (Chunge 1985; Jha 1983; Kager 1981).

Several other oral antibiotics like metronidazole and cotrimoxazole have been reported as possibly promising anti-*Leishmania* agents in the treatment of VL (R-Cuartero 1990). Some workers have questioned the efficacy of a short-term course of antibiotic rifampicin therapy with rifampicin for CL (Bygbjerg 1980). Oral azithromycin is another antibiotic effective *in vitro* and in mice but needs further investigation in human leishmaniasis (Minodier 2007). In 2002, Jiang et al (Jiang 2002) reported for the first time that omeprazole, widely used for peptic ulcer diseases, as a potential antiparasitic drug for the growth of *L. donovani* in a laboratory setting. Oral pentoxifylline, used in people with vascular diseases also has anti-*Leishmania* effects (Lessa 2001) and decreases the inflammatory reaction and resulting tissue damage (Sadeghian 2006). Pentoxifylline has a good safety profile although nausea, arthralgias, dizziness, abdominal pain and diarrhoea can occur.

Oral miltefosine, which was originally developed as an anticancer drug, is active against the *Leishmania* membrane (Croft 2006). It is currently being registered for VL in India and in Colombia for American CL (Berman 2005; Croft 2006). Miltefosine seems

active against most *Leishmania* species, but with variable efficacy depending on geographical areas, even for the same species (Soto 2004; Stojkovic 2007). The most commonly reported adverse drug reactions associated with miltefosine are transient gastrointestinal discomfort, nausea, vomiting, abdominal pain, mild elevation of liver enzymes and serum creatinine. This drug is contraindicated for use during pregnancy, and contraception is required beyond the end of treatment in women of child-bearing age (Sindermann 2006).

Promising results have been reported on the treatment of CL with oral zinc sulphate (Sharquie 1996; Sharquie 1997; Sharquie 2001). Intramuscular pentamidine (isethionate or methanesulfonate) is a conventional and costly second-line drug for treating VL in spite of being progressively abandoned due to its unacceptable toxic effects, which include damage to the pancreas (may induce irreversible insulin dependent diabetes mellitus), kidney or bone marrow (Sundar 2006). Its efficacy has also been found to have declined in India (Sundar 2006). Amphotericin B, an antifungal drug used since 1960 (Sampaio 1960), is commonly used for the treatment of American mucocutaneous leishmaniasis, HIV co-infection and VL, in areas where *Leishmania* is resistant to antimonial and pentamidine drugs (Laguna 1999; Thakur 1996; Musa 2005; Sundar 2007A; Karamian 2007; Sampaio 1997).
Oral sitamaquine is an orally active 8-aminoquinoline analogue that demonstrated efficacy in VL in different settings (Sherwood 1994) and was well tolerated. However, none of the sitamaquine dihydrochloride formulations tested *in vivo* in BALB/c mice appeared to either slow lesion progression or reduce parasite burden (Garnier 2006).

### Local treatments and non-pharmacological Interventions

Mild disease caused by *L. major* is often managed with local care alone and may not require other specific therapies. Topical and local therapies are attractive options offering reduced systemic toxicity and outpatient treatment, and are appropriate for early self-limiting lesions unlikely to cause disfigurement, restrict joint mobility or which are not at risk of dissemination.
Infiltration of skin lesions (injecting a substance directly into the infected lesion) can be very painful. Adverse effects of such intralesional (IL) treatments are: burning at the site of injection, itching, inflammation and vasovagal shock due to severe pain. A safe and efficient therapeutic method for IL injection is the use of a Dermojet device (Bogenrieder 2003). Prevention of blood-borne transmission of other infectious diseases in developing countries include reduction of injection use, implementation of blood safety practices and provision of sterile injection equipment. Antimonials are used intralesionally to limit toxicity for early non-inflamed localised lesions and are frequently used either as a few injections up to daily injections for 20 to 40 days in those with multiple or complicated lesions. Self-limiting lesions are normally amenable to weekly or alternate day IL injections of SSG or MA. According to some authors, one of the most important and common causes of treatment failure with IL antimonials are inadequate infiltration of the lesions (Faghihi 2003).
Topical formulations often offer easier administration, less adverse effects and sometimes cost effectiveness although there may be difficulties in getting enough of the active drug absorbed through the skin.
Paromomycin is an antibiotic of the aminoglycoside family originally identified as an anti-*Leishmania* drug in the 1960s and used for VL in parenteral formulations (Sundar 2007B) and for CL in topical preparations since 1987 (Asilian 1995). The names paromomycin, aminosidine, monomycin and neomycin E have been used interchangeably in the literature although the active principle is the same (Bryceson 1994). Two main topical preparations are available for CL: 15% paromomycin sulphate dissolved in a soft white paraffin base, either with 12% methylbenzethonium chloride (MBCL) or with 10% urea. The original paromomycin formulation is no longer used because of its toxicity, and new penetration-enhancing formulations have been under clinical evaluation ( Davis 2003). Of the topical preparations, paromomycin ointment has been advised as a first-line treatment in uncomplicated CL ( Asilian 2006). Adverse effects encountered were redness, pruritus, burning, oedema, local pain, inflammation, contact dermatitis, urticaria or lymphadenitis with pain. IL zinc sulphate can have a direct anti-*Leishmania* effect against *L. major* and *L. tropica* species in an *in vitro* and animal study (Najim 1998). Topical imiquimod is an immune response modifier used for the treatment of genital warts and premalignant and skin cancer conditions, which was first used in combination with antimony for American CL (Arevalo 2007). Intralesional hypertonic sodium chloride solution (HSCS) can act by its osmotic effect to destroy the parasite as well as the surrounding tissue of the granuloma (Sharquie 1995; Sharquie 1997). It seems a cheap, safe, and effective local method for treating CL. Interferon (IFN-$\gamma$) is a lymphokine originally used for the treatment of leprosy, cancer, HIV, and chronic granulomatous disease (Badaro 1990) that enhances the leishmanicidal capacity of human monocytes *in vitro* (Passwell 1986).
Photodynamic therapy (PDT) uses a form of light therapy on cells that have already been sensitised to light and is an attractive antiparasitic therapeutic intervention that offers rapid destruction of the lesion without affecting adjacent normal tissue. PDT is used in malignant skin lesions and uses porphyrin compounds locally applied, followed by the delivery of red light (Enk 2003).
A hexadecyl-phosphorylcholine (HePC) ointment appears to be useful as a topical anti-*Leishmania* preparation (Iqbal 2006). This compound which is related to miltefosine is the most promising of the new class of agents that have potent anti-*Leishmania* activity *in vitro*. Water-soluble phosphate prodrugs of buparvaquone penetrate the skin from several topical formulations making it potentially interesting for further investigation in CL.

#### Methods for promoting healing

Methods used in wound healing that include dressing and anti-

septics are often employed in ulcerative lesions of CL to accelerate cure, normalise epithelialisation and reduce scarring especially at cosmetic sites. Compromised wound healing due to repetitive trauma, contamination and infection are major problems encountered in people with OWCL and it is important to improve scar formation or at least not interfere with the natural healing process. In a recent consensus panel of recommendations for chronic and acute wound dressings (Vaneau 2007), hydrocolloid (polymer dressings with medium absorption properties and containing carboxymethylcellulose) and low-adherent dressings seem to be the most suitable dressings for the epithelialisation stage of chronic and acute wounds.

The highest impact of scarring and ulcerative lesions is on the faces of young women which exposes them to stigma and which may affect their marriage proposals (Weigel 2001; Reithinger 2005B). To assess the cosmetic impact, The Burn Scar Index (often called the Vancouver Scar Scale) is often used (Baryza 1995) to document change in scar appearance, which should be ideally measured six months after completion of treatment (Modabber 2007).

#### Physical therapies

OWCL has been treated with a range of physical methods including vaporization, cauterization, freezing, surgical excision and the application of local heat. Carbion dioxide ($CO_2$) lasers have been used to vaporize CL lesions, thereby destroying infected tissue without significant side-effects in normal tissue. A single session is usually enough and the lesion heals within three to four weeks with quite acceptable cosmetic results, although the procedure is painful and requires local anaesthetic. The efficacy of trichloroacetic acid (TCA) in the treatment of CL could be due to destroying infected tissue and skin regeneration (Nilforoushzadeh 2006). Cryotherapy, using liquid nitrogen, has been used to treat individual lesions destroying infected tissue but is labor intensive and not suitable for multiple or complicated lesions (Bassiouny 1982; Leibovici 1986; Alrajhi 2003; Minodier 2007). Laboratory studies showed that *Leishmania* parasites do not readily multiply in macrophages at temperatures greater than 39°C (Berman 1981; Sacks 1983). These findings led to studies investigating the efficacy of thermotherapy treatment of VL with hot-water baths (Neva 1984), infrared light (Junaid 1986), direct-current electrical stimulation (Sharquie 1998), ultrasound (Aram 1987), laser (Rodriguez 1990; Babajev 1991; Meawad 1997; Asilian 2004B) and radio-frequency waves (Navin 1990; V-Castrejon 1997; Levine 1992). The procedure is painful and may require local anaesthetic (Sadeghian 2007). Excision of lesions is not generally recommended because of the high risk of local relapse and disfiguration (Markle 2004).

#### Alternative therapies

The reason for seeking alternative therapies is the increase in treatment failure with antimonial drugs. Perhaps 80% of the world's population rely solely upon medicinal plants as the source of remedies for treatment of the disease. Modern drugs are simply not available or expensive. Herbal remedies or honey have been used for a long period of time in both traditional and modern medicine in Iran (Nilforoushzadeh 2007; Zerehsaz 1999). Different plants of medicinal value (*Azadirachta indica*, *Acacia nilotica*, and *Allium sativa*) traditionally used in the west and central parts of Sudan revealed to have active anti-*Leishmania* activity on *L. major* promastigotes *in vitro* (Khalid 2005). Honey is effective in wound healing through improvement of granulation and epithelialisation stages, improvement of debridement and reduction of wound malodor (Moore 2001; Pieper 2003). Studies have shown that honey produced from flowers in Australia and New Zealand has antibacterial properties (Pieper 2003).

### Why it is important to do this review

Control of CL depends currently on early detection and rapid treatment. The mainstays of treatment have been pentavalent antimonials but other oral and topical treatment alternatives have become available in recent years. Global health development policies have been mainly focused on new and innovative research to develop effective and affordable tools to tackle neglected tropical diseases (NTDs) and provide necessary new knowledge. The WHO is now prioritising the delivery of drugs which are currently available and using existing resources for the reduction of mortality, morbidity and disability as a result of NTDs in low-income countries (Savioli 2006). However, to improve existing control of disease, the evidence for the effectiveness of different treatment strategies is needed as well as comparisons for safety and cost-effectiveness.

This systematic review focused on addressing the effects of treatments for the localized form of CL due to *L. tropica* and *L. major* accounting for more than 90% of CL in the Old World. Since the great majority of cases of OWCL heal spontaneously within 3 to 18 months, the rationale for the use of systemic and topical treatments needs to be well established and preferably stratified for different geographic regions and *Leishmania* species. Treatments for American CL and prevention measures for all types of cutaneous and mucosal leishmaniasis will be addressed in separate Cochrane reviews.

## OBJECTIVES

To assess the effects of therapeutic interventions for the localised form of CL in the Old World.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials.

### Types of participants

All immuno-competent people who have localised OWCL confirmed by parasitological diagnostic methods, i.e. tissue smears, histology, culture or polymerase chain reaction (PCR).

### Types of interventions

The interventions were either single therapy, or combination therapy. The comparators were either no treatment, vehicle only, or another active compound.

**1. Systemic and intralesional antimonials**

**1.1 Meglumine Antimoniate (Glucantime)**

**1.2 Stibogluconate**

**2. Non-antimonial systemic treatments**

**2.1 Oral antifungals**

**2.2 Oral dapsone**

*2.3 Oral allopurinol*

**2.4 Oral antibiotics**

**2.5 Oral pentoxifylline**

**2.6 Oral miltefosine**

**2.7 Oral zinc sulphate**

**3. Non-antimonial topical or intralesional therapies**

**3.1 Topical antifungals**

**3.2 Topical paromomycin (aminosidine)**

**3.3 Intralesional zinc sulphate**

**3.4 Topical imiquimod**

**3.5 Intralesional hypertonic sodium chloride**

**3.6 Intralesional interferon-gamma (IFN-$\gamma$)**

**3.7 Topical photodynamic therapy**

**4. Measures for promoting healing**

**5. Physical therapies**

**5.1 Laser**

**5.2 Trichloroacetic acid**

**5.3 Cryotherapy**

**5.4 Thermotherapy**

**6. Alternative therapies**

### Types of outcome measures

#### Primary outcomes

- Percentage of lesions cured around three months after the end of treatment.
- Percentage of participants with a complete cure around three months after the end of treatment.

By cured, we meant that all inflammatory signs disappeared (either skin oedema or hardening, or both) and that complete scarring or healthy repair occurred in ulcerative lesions. Lesions were not considered to be healed if there was no re-epithelialised skin, or if inflammatory signs remained after follow-up.
We found the majority of RCTs included in this review assessed participants instead of lesions as the unit of analysis.
We considered that a period of at least three months after treatment was needed to reflect the minimum time period for assessing outcomes given that most relapses occur within three to six months after successful treatment (Khan 2005).

#### Secondary outcomes

- Speed of healing (time taken to be 'cured')
- Duration of remission and percentage of people with treated lesions that recur within six months, one, two and three years
- Degree of functional and aesthetic impairment
- Prevention of scarring
- Quality of life
- Adverse effects

#### Tertiary outcomes

- Change in ability to detect *Leishmania* by parasitological diagnostic methods (e.g. smear, PCR or culture)
- Emergence of resistance (defined as a decline in the efficacy of a drug against a population of parasites previously susceptible to that compound (Ponte-Sucre 2003).The definition assumes that the original susceptibility of the population is known, which is not always the case for *Leishmania*)
- Microbiological or histopathological cure of skin lesions
- Development of cell-mediated immunity (i.e. positive leishmanin skin test)

## Search methods for identification of studies

### Electronic searches

We searched the Cochrane Skin Group Specialised Register in April 2008 using the following terms:
(solitary or limited or (old and world) or localised) AND (*cutaneous and leishmania*)
We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 2, 2008) using the following strategy:
#1(cutaneous leishmania*):ti,ab,kw
#2MeSH descriptor Leishmaniasis, Cutaneous, this term only
#3(solitary or limited or localised or (old world)):ti,ab,kw
#4(#1 OR #2)
#5(#3 AND #4)
#6SR-SKIN

#7(#5 AND NOT #6)
We searched MEDLINE (OVID) and MEDLINE(R) In-Process (from 2003 to April 2008) using the strategy in Appendix 1
We searched EMBASE (OVID) (from 2005 to April 2008) using the search strategy in Appendix 2
The UK Cochrane Centre 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 CINAHL (from 1982 to 29 th August 2007) using the search strategy in Appendix 3
We searched LILACS (Latin American and Caribbean Health Sciences) on http://bases.bireme.br (from inception to April 2008) using the search strategy in Appendix 4
We searched the American College of Physicians (ACP) journal club (from 1991 to May 2007) using the terms: cutaneous and leishmaniasis.

#### Ongoing Trials Databases

In August 2007 we searched the following ongoing trials registers using the terms "cutaneous leishmaniasis":

- The metaRegister of Controlled trials on www.controlled-trials.com
- The US National Institutes of Health Register on www.clinicaltrials.gov
- The Ongoing Skin Trials Register on www.nottingham.ac.uk/ongoingskintrials
- The Australian and New Zealand Clinical Trials Registry on www.anzctr.org.au
- The World Health Organisation International Clinical Trials Registry platform on www.who.int/trialsearch

### Searching other resources

#### References from unpublished studies

We searched the bibliographies of all papers identified by these strategies and obtained the relevant articles.

#### Unpublished literature

We wrote to National Programme Managers, General Coordinators, Directors, Clinicians, WHO-EMRO Regional Officers of endemic countries, pharmaceutical companies and authors for further information about unpublished and ongoing trials.

We contacted the following Tropical Medicine Centres:
Department of Infectious Diseases and Tropical Medicine at the University of Munich, Germany;
Swiss Tropical Institute, Switzerland; Prince Leopold Institute of Tropical Medicine, Belgium;
McGill Centre for Tropical Disease, Canada;
Tulane University School of Public Health & Tropical Medicine, USA;
London School of Hygiene & Tropical Medicine, UK;
Tropical Medicine at the Liverpool School of Tropical Medicine, UK;
Department of Public Health and Tropical Medicine James Cook, University of North Queensland, Australia;
Institut Pasteur, France;
Bernhard Nocht Institute, Germany;
TropEdEurop, Spain.
However, no response was obtained from some institutions and no additional trials were sought.

#### Adverse Effects

A MEDLINE search (from 1950 to 2007) was made for adverse or side effects using the search strategy in Appendix 5.

#### Other

There were no language restrictions when searching for publications. Eligible RCTs were included regardless of the language of publication of their report.

## Data collection and analysis

### Selection of studies

We checked the titles and abstracts identified from the searches by at least two authors (UG, MP, LR). If it was unclear, then two authors obtained the full text study for independent assessment (UG, MP, LR). The authors decided which trials fitted the inclusion criteria. The authors resolved any disagreements by discussion, with referral to a third author (UG) if necessary. Excluded studies and reasons for exclusion are stated in the Characteristics of excluded studies.

### Data extraction and management

At least two independent authors carried out data extraction (MC, UG, MP, LR) using a pre-designed data extraction form. We extracted data for all outcomes for all relevant drugs, paying attention particularly to the doses and therapy frequencies. We resolved disagreements by discussion. We obtained the missing data from trial authors when possible. The time periods reported in the included trials were not always exactly at three months after treatment (but all were at least 2 months post-treatment).

### 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):

- the method of generation of the randomisation sequence
- the method of allocation concealment - it will be considered 'adequate' if the assignment cannot be foreseen

- who was blinded / not blinded (participants, clinicians, outcome assessors)
- how many participants were lost to follow up in each arm (split into post-randomisation exclusions and later losses if possible), and whether participants were analysed in the groups to which they were originally randomised (intention to treat)

In addition the quality assessment also included:

- sample size calculation declared
- inclusion and exclusion criteria defined
- reporting of *Leishmania* species involved
- time of follow-up
- baseline comparability of severity of infection, age, sex and duration of complaint
- conflict of interest

The information was recorded in the risk of bias table ( Characteristics of included studies) and a description of the quality of each study was given based on these components.

### Subgroup analysis and investigation of heterogeneity

The results were expressed as Relative Risk (RR and 95% confidence intervals (CI)) for dichotomous outcomes. We did not find any paper with continuous outcomes. The percentage of lesions 'cured' at three months after the end of treatment was the primary outcome measure if available. If this was not available, secondary and tertiary outcomes were used. To estimate differences between treatments we pooled trials that evaluate similar interventions and controls and calculated a weighted treatment effect across trials, using a random effects model. Where it was not possible to perform a meta-analysis, the data has been summarised for each trial. Only six of the trials explicitly stated intention-to-treat (ITT) analysis. Where an ITT was not stated, we used the numbers originally randomised to the groups in order to calculate effect estimates.
No substantial heterogeneity ($I^2$ > 50%) existed in the one pooled analysis of 2 studies for the primary outcome. We did not therefore progress to undertake sensitivity or subgroup analyses according to high risk of bias, *Leishmania* species, location and severity of infection, geographical setting, diagnostic techniques, type of treatment (topical, systemic or combination), and relapse or re-infection.
Cross-over trials were not considered in this review because they are an inappropriate design for treatments which can potentially cure an infectious disease. Quasi-randomised and non-randomised controlled studies were listed but not discussed further in Table 1.
We did not find any particular additional important information in the specific search for terms of adverse effects and for every particular treatment. They were described qualitatively in the sections of results and discussion.

**Table 1. Quasi-randomised, non-randomised or uncontrolled studies**

| Authors | Title | Journal | Observations | Number of participants |
|---|---|---|---|---|
| Akuffo H, Dietz M, Teklemariam S, Tadesse T, Amare G, Yermane Berhan T | The use of itraconazole in the treatment of leishmaniasis caused by Leishmania aethiopica | Trans R Soc Trop Med & Hyg 1990; 84: 532-534 | Quasi-randomised trial | 14 |
| Al-Waiz M, Sharique KE, Al-Assir M | Treatment of cutaneous leishmaniasis by intralesional metronidazole | Saudi Med J 2004; 25 (10): 1512-1513 | Non-randomised trial | 73 |
| Asilian A, Sadeghinia A, Faghihi G, Momeni A, Amini Harandi A | The efficacy of treatment with intralesional meglumine antimoniate alone, compared with that of cryotherapy combined with the meglumine antimoniate or intrale-<br>sional sodium stiboglu- | Ann Trop Med Parasitol 2003; 97 (5): 493-498 | Non-randomised trial | 180 |

**Table 1. Quasi-randomised, non-randomised or uncontrolled studies** (*Continued*)

| | | | | |
|---|---|---|---|---|
| | conate, in the treatment of cutaneous leishmaniasis | | | |
| Daoud S, Boushi L | Azithromycin, ineffective in the treatment of old-world cutaneous leishmaniasis | Int J Dermatol 2006; 45: 1126-1128 | Non-randomised trial | 45 |
| El-Darouti MA, Al-Rubaie SM | Cutaneous leishmaniasis: treatment with combined cryotherapy and intralesional stibogluconate injection | Int J Dermatol 1990; 29(1): 56-9 | Non-randomised trial | 44 |
| El-Safi SH, Murphy AG, Bryceson ADM, Neal RA | A double-blind clinical trial of the treatment of cutaneous leishmaniasis with paromomycin ointment | Trans R Soc Trop Med & Hyg 1990; 84: 690-691 | Quasi-randomised trial (double-blinded study) | 40 |
| Gurei MS, Tatli N, Ozbilge H, Erel O, Seyrek A, Kocygit A, Ulukanligil M | Efficacy of cryotherapy and intralesional pentostam in treatment of cutaneous leishmaniasis | J Egypt S Parasitol 2000; 30 (1): 169-176 | Non-randomised trial | 97 |
| Hellier I, Dereure O, Tournillac I, Pratlong F, Guillot B, Dedet JP, Guilhou JJ | Treatment of old world cutaneous leishmaniasis by pentamidine isethionate | Dermatology 2000; 200 (2): 120-123 | Non-randomised trial | 11 |
| Kocygit A, Gur S, Gurel MS, Bulut V, Ulukanligil M | Antimonial therapy induces circulating pro inflammatory cytokines in participants with cutaneous leishmaniasis | IAI 2002; 70 (12): 6589-6591 | Non-randomised trial | 52 |
| Livshin R, Weinrauch L, Even-Paz Z, El-On J | Efficacy of rifampicin and isoniazid in cutaneous leishmaniasis | Int J Dermatol 1987; 26 (1): 55-9 | Non-randomised trial | 39 |
| Meymandi S, Holmes D, Crawford RI | Comparative study of the efficacy of combined imiquimod (Aldara T) 5% cream and intrale- | J Eur Acad Dermatol Venereol 2005; 19 (2): 38 | Non-randomised trial | 99 |

**Table 1. Quasi-randomised, non-randomised or uncontrolled studies** (*Continued*)

| | | | | |
|---|---|---|---|---|
| | sional meglumine antimoniate (Glucantime) | | | |
| Ozgostasi O, Kirtak N, Erbagci Z | Cryotherapy in the treatment of cutaneous leishmaniasis | J Dermatol Treat 1997; 8: 179-182 | Non-randomised trial | 64 |
| Pareek SS | Combination therapy of sodium stibogluconate and rifampicin in cutaneous leishmaniasis | Int J Dermatol 1984; 23(1): 70-1 | Non-randomised trial | 32 |
| Sharquie KE, Al-Hamamy H, El-Yassin D | Treatment of cutaneous leishmaniasis by direct current electrotherapy: the baghdadin device | J Dermatol 1998; 25: 234-237 | Non-randomised trial | 69 |
| Vardy D, Barenholz Y, Cohen R, Zvulunov A, Biton A, Klaus S, Frankenburg S | Topical amphotericin B for cutaneous leishmaniasis | Arch Dermatol 1999; 135 (7): 856-857 | Non-randomised trial | 13 |
| Vardy D, Barenholz Y, Naftoliev N, Kaus S, Gilead L, Frankenburg S | Efficacious topical treatment for human cutaneous leishmaniasis with ethanolic lipid amphotericin B | Trans R Soc Trop Med & Hyg 2001; 95: 184-186 | Non-randomised trial (but single-blinded for the participant) | 19 |
| Radmanesh M, Falahzadeh A, Dowraghi HF | Weekly versus every 3 days intralesional meglumine antimoniate therapy for cutaneous leishmaniasis | J Dermatolog Treat 1998; 9(4): 231-233 | Non-randomised trial | 70 |
| Mapar MA, Kavoosi H, Dabbagh MA | Assessment of the effect of topical opium in treatment of cutaneous leishmaniasis | Iranian J Dermatol 2001; 4(4): 23-28. | Non-randomised trial | 96 |
| Seeberger J, Daoud S, Pammer J | Transient effect of topical treatment of cutaneous leishmaniasis with imiquimod. | Int J Dermatol. 2003;42(7): 576-9 | Non-randomised trial | 15 |

**Table 1. Quasi-randomised, non-randomised or uncontrolled studies** (*Continued*)

| | | | | |
|---|---|---|---|---|
| Bahamdan KA, Tallab TM, Johargi H, Nourad MM, Ibrahim K, el Sherbini AH, Karkashan E, Khare AK, Nauri MM | Terbinafine in the treatment of cutaneous leishmaniasis: a pilot study | Int J Dermatol. 1997; 36(1): 59-60 | Uncontrolled | 27 |
| Morizot G, Delgiudice P, Caumes E, Laffitte E, Marty P, Dupuy A, Sarfati C, Hadj-Rabia S, Darie H, LE Guern AS, Salah AB, Pratlong F, Dedet JP, Grogl M, Buffet PA | Healing of Old World cutaneous leishmaniasis in travelers treated with fluconazole: drug effect or spontaneous evolution? | Am J Trop Med & Hyg 2007; 76(1): 48-52 | Uncontrolled | 35 |
| Leibovici V, Aram H | Cryotherapy in acute cutaneous leishmaniasis | Int J Dermatol. 1986;25(7): 473-5 | Uncontrolled | 14 |
| Aram H, Leibovici V | Ultrasound-induced hyperthermia in the treatment of cutaneous leishmaniasis | Cutis. 1987;40(4): 350-3 | Uncontrolled | 18 |
| Junaid AJ | Treatment of cutaneous leishmaniasis with infrared heat | Int J Dermatol. 1986;25(7): 470-2 | Uncontrolled | 178 |
| Faris RM, Jarallah JS, Khoja TA, al-Yamani MJ | Intralesional treatment of cutaneous leishmaniasis with sodium stibogluconate antimony | Int J Dermatol. 1993;32(8): 610-2 | Uncontrolled | 710 |
| Joshi RK, Nambiar PM | Dermal leishmaniasis and rifampicin | Int J Dermatol. 1989;28(9): 612-4 | Uncontrolled | 15 |
| Abahusein A, Larbi EB, al-Khawajah A, al-Gindan Y, Jain S | Evaluation of topical ketoconazole in cutaneous leishmaniasis | East Afr Med J. 1992;69(1): 14-7 | Uncontrolled | 10 |
| Sharquie KE, Al-Talib KK, Chu C | Intralesional therapy of cutaneous leishmaniasis with sodium stibogluconate antimony | Br J Dermatol 1988; 119: 53-57. | Non-randomised trial | 60 |

**Table 1. Quasi-randomised, non-randomised or uncontrolled studies** (*Continued*)

| | | | | |
|---|---|---|---|---|
| Van den Enden E, Van Gompel A, Stevens A, Vandeghinste N, Le Ray D, Gigase P, De Beule K, Van den Ende J | Treatment of cutaneous leishmaniasis with oral itraconazole | Int J Dermatol 1994; 33(4): 285-286. | Uncontrolled | 22 |
| Tallab TM, Bahamdam KA, Mirdad S, Johargi H, Mourad MM, Ibrahim K, el Sherbini AH, Karkashan E, Khare AK, Jamal A | Cutaneous leishmaniasis: schedules for intralesional treatment with sodium stibogluconate | Int J Dermatol 1996; 35(8): 594-597. | Uncontrolled | 96 |
| Jabbar A, Junaid N | Treatment of cutaneous leishmaniasis with infrared heat | Int J Dermatol 1986; 25(7): 470-472. | Uncontrolled | 178 |

# RESULTS

## Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting assessment; Characteristics of ongoing studies.

### Results of the search

We identified 60 studies from our searches, of which we included 49 that overall randomised 5559 participants. We excluded seven studies which are presented in the Characteristics of excluded studies table. We found three studies that are ongoing trials and one awaiting assessment which are listed in Characteristics of ongoing studies and Characteristics of studies awaiting classification tables, respectively. We will include these studies in future updates of this review.

We found one article published in several journals describing the same study (Nilforoushzadeh 2006); these are grouped together in the included study reference of the above mentioned primary paper.

This review focused on *L. major* and *L. tropica* infections because of the absence of studies involving other species such as *L. infantum, L. aethiopica* or *L. donovani.*

## Included studies

The 49 included studies (of which 22 were placebo-controlled and 27 had active controls) are detailed in the Characteristics of included studies table.

The studies included in this review were conducted throughout different countries, mainly in the Far or Middle East, except for two that were conducted in Africa (Sudan and Tunisia) and one in Turkey. Twenty-seven were carried out in Iran, two in Pakistan, four in Saudi Arabia, two in Kuwait, two in Iraq, two in Syria, one in Afghanistan and six in India.

### 1. Systemic and intralesional antimonials

#### 1.1 Meglumine Antimoniate (Glucantime)

One RCT from Pakistan (Mujtaba 1999) used intralesional (IL) meglumine antimoniate (MA) weekly until complete cure of lesions or up to 8 weeks on 49 participants with 111 lesions, and ILMA fortnightly until complete cure of lesions or up to 8 weeks on 47 participants (ITT = 55) with 104 lesions. The *Leishmania* species were not reported. Another RCT from Saudi Arabia (Alkhawajah 1997) compared up to 12 IM injections of 15 mg/kg/day MA for 6 days a week on 40 participants (with 77 lesions) and ILMA 0.2 to 0.8 ml every other day over 30 day period on 40 participants (with 70 lesions). The *Leishmania* species found in the area was *L. major.*

#### 1.2 Stibogluconate (Pentostam)

A RCT (Reithinger 2005) of 431 participants infected with *L. tropica* in Afghanistan compared 148 participants treated with IL SSG (a total of 5 injections of 2 to 5 ml every 5 to 7 days depending on the lesion size) for up to 29 days, with 144 participants treated with IM SSG (20 mg/kg) daily for 21 days, and with 139 participants treated with thermotherapy using radiofrequency waves.

We also found 24 RCTs using antimonials either as the control group or as a combined treatment with other interventions, 21 of which are referred to in this section on 'Included studies', 2 in

the 'Ongoing studies' and 1 in the 'Studies awaiting classification' reference lists.

### 2. Non-antimonial systemic treatments

#### 2.1 Oral antifungals

There were two trials on the use of ketoconazole. One trial from Kuwait where the *Leishmania* species was not mentioned (Alsaleh 1995) compared 18 participants treated with oral 600 mg/day ketoconazole for 6 weeks maximum and 15 participants treated with 800 mg/day of ketoconazole for the same time period. The other trial from Iran with participants infected with *L. tropica* and *L. major* (Salmanpour 2001), compared 32 participants treated with ILMA 6 to 8 injections biweekly with 64 participants treated with oral ketoconazole (adults 600 mg/day and children 10 mg/kg/day) for 30 days.

There were six trials on the use of itraconazole in OWCL. Two studies from Iran where participants were infected with *L. major*: in one trial (Momeni 1996) oral itraconazole 7 mg/kg/day for 3 weeks (max. 400 mg/kg/d) in 70 participants was compared with placebo in 70 participants; in the other trial (Nassiri-Kashani 2005) 100 participants treated with oral itraconazole 200 mg/day for 8 weeks were compared with 100 participants treated with placebo. A trial from Kuwait (Al-Fouzan 1991) of 24 participants infected with *L. tropica* or *L. major;* 15 participants were given oral itraconazole, 100 mg/twice per day (12 year-old participants were given 3 mg/kg/day) for 6 to 8 weeks and 9 participants were given placebo for 6 to 8 weeks. There were three trials using itraconazole in participants from India with *L. tropica* infections (or at least this was the *Leishmania* species found in the area). The first trial (Dogra 1990) compared 15 participants treated with 4 mg/kg/day of oral itraconazole for 6 weeks (max. of 200 mg/day) with 5 untreated participants. The second trial (Dogra 1992) compared 20 participants treated with itraconazole 4 mg/kg/day (max. 200 mg/day) for 6 weeks with 20 participants treated with dapsone 4 mg/Kg in 2 doses per day for 6 weeks and another 20 participants with placebo. The third trial (Dogra 1996) compared 10 participants treated with oral itraconazole 100 mg, twice per day, for 6 weeks with another 10 participants who were given placebo.

There were two studies on the use of oral fluconazole in OWCL. One trial from Saudi Arabia (Alrajhi 2002) of participants infected with *L. major* compared 200 mg/day oral fluconazole for 6 weeks in 106 participants and placebo in 103 participants. The other trial from Aleppo-Syria and *L. tropica* infections (Dandashi 2005) compared 46 participants (264 lesions) treated with 200 mg/day oral fluconazole for 6 weeks and 19 participants (102 lesions) with placebo.

#### 2.2 Oral dapsone

There were two studies on the use of dapsone on participants from India where *L. tropica* was endemic. In 1 trial (Dogra 1991) 60 participants were treated with 100 mg dapsone tablets, every 12 hours for 6 weeks and 60 participants with placebo. In the other study already mentioned in the oral antifungals section compared oral dapsone with oral itraconazole and placebo (Dogra 1992).

#### 2.3 Oral allopurinol

There were three trials using oral allopurinol alone or combined with antimonials in different species of *Leishmania*. A trial from Iran (Esfandiarpour 2002) with *L. tropica* which is present in that country compared 50 participants treated with oral 15 mg/kg/day allopurinol for 3 weeks, 50 participants treated with IM 30 mg/kg/day MA for 2 weeks, and another 50 participants treated with allopurinol plus MA same doses simultaneously. A trial conducted in an army camp from Iran with participants infected with *L. major* (Momeni 2002) compared 36 participants treated with oral 20 mg/kg/day allopurinol plus low-dose 30 mg/kg/day IMMA for 20 days, and 36 participants with 105 lesions treated with 60 mg/kg/day IMMA for 20 days. A trial from the army in Pakistan (Mashood 2001) compared 20 participants treated with 20 mg/kg/day oral allopurinol in 3 to 4 doses for 15 days and 20 participants treated with IV 20 mg/kg/day SSG for 15 days. In this trial the *Leishmania* species was not reported.

#### 2.4 Oral antibiotics

There were two trials using oral rifampicin in *L. tropica* infections from India (Kochar 2000, Kochar 2006). In 1 trial (Kochar 2000) 25 participants treated with rifampicin 1200 mg/day in 2 divided doses for 4 weeks were compared with 25 participants who received placebo. The other trial (Kochar 2006) compared 25 participants treated with rifampicin 1200 mg/day in 2 divided doses plus omeprazole 20 mg for 6 weeks with 25 participants treated with placebo.

There was 1 trial from Saudi Arabia where the *Leishmania* species was not reported (Jaffar 2006) which compared 46 participants treated with rifampicin orally in a dose of 10 mg/kg/d in 2 equally divided doses during meals for 4 to 6 weeks, and 16 participants with placebo.

We found no RCTs using other antibiotics.

#### 2.5 Oral pentoxifylline

There was one trial (Sadeghian 2006) using oral pentoxifylline on participants from Iran with *Leishmania* species not characterised where 64 participants were randomised to IMMA 20 mg/kg/day plus pentoxifylline orally (400 mg) or IMMA 20 mg/kg/day plus placebo, both 3 times daily for 20 days.

#### 2.6 Oral miltefosine

There was 1 trial (Mohebali 2007) using oral miltefosine in participants from Iran infected with *L. major* where 63 participants were randomised to oral miltefosine at a dosage of 2.5 mg/kg/d for 28 days or IMMA at a dosage of 20 mg/kg/d for 14 days.

### 2.7 Oral zinc sulphate

There was 1 trial (Sharquie 2001) using oral zinc sulphate that compared 130 participants from Iraq infected with *L. major* and *L. tropica*. Thirty-nine participants were treated with 2.5 mg/kg zinc sulphate orally, 1 capsule every 8 hours; 37 participants were treated with 5 mg/kg zinc sulphate orally, 1 capsule every 8 hours; and 39 participants were treated with 10 mg/kg zinc sulphate orally, 1 capsule every 8 hours; and 15 participants were left as controls.

## 3. Non-antimonial topical or intralesional therapies

### 3.1 Topical antifungals

There were two trials using topical antifungals in OWCL. One trial from Saudi Arabia where *L. major* is present (Larbi 1995) compared 31 participants (62 lesions) treated with 2% miconazole cream, twice per day, for 30 days and 31 participants (89 lesions) treated with 1% clotrimazole cream, twice per day, also for 30 days. Another trial from Iran (Momeni 2003) compared 45 participants treated with topical 2% ketoconazole 25 g twice per day for 21 days and 45 participants with placebo in subjects infected with *L. major* and *L. tropica.*

### 3.2 Topical paromomycin (aminosidine)

There were nine studies using topical paromomycin for OWCL.
One trial from Iran (Asilian 1995) of participants infected with *L. major* and *L. tropica* compared 126 participants treated with 15% paromomycin and 10% urea, twice a day for 14 days and 125 participants treated with placebo.
Five trials were conducted in participants with *L. major* infections, four of which were conducted in Iran: (Asilian 2003) compared 117 participants treated with 2 applications per day of paromomycin ointment and 116 participants treated with 1 application per day, both for a 4 week treatment, (Asilian 2006) compared 20 participants treated with 15% paromomycin and 12% methylbenzethonium chloride (MBCL) applied topically twice daily for 28 days, 20 participants treated with photodynamic therapy (PDT) every week for 4 weeks and 20 participants with topical placebo, (Faghihi 2003) 48 participants were treated with 15% paromomycin (sulphate) and 10% urea ointment, twice per day, for a mean duration of 45 days and a maximum duration of 3 months and IL 1.5 g/5ml MA weekly (maximum 12 injections and mean number of injections 5 for each lesion) and (Shazad 2005) compared 30 participants treated with paromomycin ointment 0.5 mg/mm$^2$ twice a day for 20 days with 30 participants treated with ILMA (dose unspecified) every other day for 20 days. The fifth trial which was from Tunisia (Ben- Salah 1995) compared 66 participants treated with 15% paromomycin and 10% urea twice per day for 14 days and 66 participants treated with placebo.
In a trial from Iran (Iraji 2005) the *Leishmania* species were not defined. Forty participants were treated with topical 15% paromomycin sulphate mixed with urea twice daily for 30 days and another 40 were treated with placebo.
There was a trial from Turkey (Özgöztasi 1997) where *L. tropica* was endemic in the area compared 40 participants treated with topical 15% paromomycin (sulphate) and 12% MBCL twice per day for 15 days with 32 participants treated with 400 mg/day oral ketoconazole for 30 days (dosage was reduced to 200 mg if participants were under the age of 12 years).

### 3.3 Intralesional zinc sulphate.

We found three trials on the use of IL zinc sulphate in *L. major* infections. A trial from Iraq (Sharquie 1997) where *L. major* and *L. tropica* were found in the area, compared 19 participants treated with an IL 2% zinc sulphate solution, 17 participants treated with IL hypertonic 7% sodium chloride solution (frequency of dosages were not clearly reported) with 18 participants treated with IL 100 mg/ml SSG. Nine participants were left as controls. Another trial from Iran (Iraji 2004) compared 49 participants with 1 IL injection (0.1 to 4ml) of 2% zinc sulphate and 55 participants treated with 1 IMMA injection (0.1 to 4 ml and occasionally more). Another trial from Iran (Firooz 2005) compared 36 participants treated with 6 weekly IL injections of 2% zinc sulphate and 36 participants treated with 6 weekly ILMA injections.

### 3.4 Topical imiquimod

There was one trial (Firooz 2006) using topical imiquimod in participants from Iran where *L. tropica* was endemic. This trial compared 59 participants treated with 5% imiquimod cream 3 times per week for 28 days plus 20 mg/kg/d IMMA for 14 days and 60 participants treated with placebo cream plus IMMA at the same regimen.

### 3.5 Intralesional hypertonic sodium chloride

There were two trials using IL hypertonic sodium chloride (HSCS) in *L. major* infections endemic in the area. One trial from Iraq compared IL 7% HSCS with IL SSG and is already mentioned in the IL zinc sulphate section (Sharquie 1997). Another study from Iran (Sadeghian 2006B) compared 36 participants treated with IL 5% HSCS (0.5 to 1 ml) and 36 participants treated with ILMA (0.5 to 1 ml), both groups for 6 to 10 weeks.

### 3.6 Intralesional interferon-gamma (IFN-$\gamma$)

There was one RCT using intralesional interferon-gamma (IFN-$\gamma$) in participants from Syria with *L. tropica* infections (Harms 1991). This trial compared 20 participants treated with IL IFN-$\gamma$ (25 mg) and 20 participants treated with ILMA 1 to 3 ml, both groups once weekly for 5 weeks.

### 3.7 Topical photodynamic therapy

We found one trial from Iran with *L. major* infections (Asilian 2006) already mentioned under the topical paromomycin section.

#### 4. Measures for promoting healing

We found no RCTs on measures for promoting healing. However, 1 trial that recruited schoolchildren from Sudan (Lynen 1992) compared 2 antiseptic chemicals: 35 participants were treated with diminazene aceturate (Berenil) and 35 participants were treated with a solution of cetrimide and chlorhexidine (Savlon), both groups for 50 days. The parasite was not identified.

#### 5. Physical therapies

There were seven trials using different physical therapies including $CO_2$ laser, trichloroacetic acid, cryotherapy and thermotherapy with radiofrequency waves.

### 5.1 Laser

There was a trial from Iran (Asilian 2004B) comparing 123 participants treated with $CO_2$ laser (30 W, continuous) applied to the lesion, with 110 participants treated with IMMA at a dosage of 50 mg/kg/d for 15 days (after 15 days of rest, this treatment was repeated). The *Leishmania* species was not mentioned.

### 5.2 Trichloroacetic acid (TCA)

A RCT from Iran (Nilforoushzadeh 2006) compared 40 participants treated with 50% TCA applied on the lesions every 2 weeks either until complete re-epithelialization of the lesions occurred or for up to 3 sessions, with 40 participants treated with ILMA weekly until complete re-epithelialization of the lesions occurred or for up to 6 weeks. The *Leishmania* species was not mentioned.

### 5.3 Cryotherapy

There were three trials from Iran (*Leishmania* species not reported) using cryotherapy alone or combined with antimonials. One trial (Asilian 2004A) compared 100 participants treated with cryotherapy and ILMA every 2 weeks, 200 participants treated with cryotherapy every 2 weeks and 100 participants treated with ILMA injections every 2 weeks. Another trial (Nilforoushzadeh 2004) compared 81 participants treated with ILMA twice every week until complete healing or for a maximum of 6 weeks and 76 participants treated with a combined triple therapy consisting of 15% paromomycin, cryotherapy and ILMA. The third trial ( Salmanpour 2006) compared 20 participants treated with a combination of cryotherapy and ILMA, 20 participants treated with cryotherapy (liquid nitrogen) applied twice to the lesion with a cotton applicator and 20 participants treated with ILMA weekly for a total of 6 to 8 times for each case.

### 5.4 Thermotherapy

There was a trial which is already mentioned in the antimonials section that compared antimonials with thermotherapy. One hundred and thirty-nine participants were treated with thermotherapy using radiofrequency waves consisting of 1 treatment of several consecutive applications at 50°C for 30s depending on lesion size (Reithinger 2005). Another trial (Sadeghian 2007) performed in 117 participants in Iran (*Leishmania* species not mentioned) compared 57 participants treated with controlled localised heating at 50°C surface temperature for 30s (controlled with a digital thermometer) once weekly for 4 consecutive weeks and 60 participants treated with ILMA once weekly for 4 consecutive weeks.

#### 6. Alternative therapies

We found three trials conducted in Iran using alternative therapies such as a topical herbal extract, garlic cream, and topical honey.
A trial (Zerehsaz 1999) compared 86 participants treated with a dressing of topical herbal extract (Z-HE) for 5 days plus IM placebo for 20 days and 85 participants treated with 20 mg/kg/day IMMA 15 for 20 days plus topical placebo for 5 days. The *Leishmania* species was not mentioned.
A trial (Gholami 2000) of participants infected with *L. major,* compared 96 participants with 5% garlic cream for 3 weeks with placebo treatment in 75 participants.
A trial (Nilforoushzadeh 2007) from Iran compared 50 participants treated with dressing of topical honey twice daily plus ILMA once weekly until complete healing of the ulcer or for maximum of 6 weeks, with 50 participants treated with ILMA monotherapy. The *Leishmania* species was not mentioned.

## Excluded studies

There were seven RCTs which we excluded, details of which are in the Characteristics of excluded studies table. We have excluded them for several reasons:
participants were randomly selected but not randomly assigned to the treatment groups;
although the authors stated that the RCT was randomised, the method of generation of randomisation sequence was inappropriate;
cross-over studies;
no assessment of clinical primary outcomes.

### Ongoing studies

We identified three ongoing studies from trials registers ( ISRCTN32701387; NCT00480883; NCT00606580). These are evaluating topical WR 279.396 *vs.* topical paromomycin *vs.* placebo, standard dose of IMMA *vs.* low dose IMMA plus oral allopurinol, and oral omeprazole plus low dose of IMMA *vs.* low and standard doses of MA plus placebo. We will evaluate them in a future update of this review.

### Studies awaiting assessment

There is one study which is awaiting assessment (Layegh 2007) because it was published just after closing the search of trials. This RCT assessed oral azithromycin and IMMA (Characteristics of studies awaiting classification).

## Risk of bias in included studies

Our assessment of the risk of bias in the included studies has broadly followed the criteria set in the protocol. We thought the quality of the RCTs was generally poor for the following reasons:

### Allocation

There were only 17 studies where the method of generation of the randomisation sequence was clearly stated (Characteristics of included studies).

Only six of the included studies (Alrajhi 2002; Asilian 2006; Ben-Salah 1995; Firooz 2005; Firooz 2006; Nassiri-Kashani 2005) had an adequate reporting of the method of allocation concealment (see Characteristics of included studies for details).

Only four studies reported both an adequate generation of randomisation sequence and an adequate method of allocation concealment (Alrajhi 2002; Firooz 2005; Firooz 2006; Nassiri-Kashani 2005).

### Blinding

Twenty-one RCTs included in this review were double-blinded; 3 were single-blinded and 25 did not use any blinding at all or at least did not mention it. See Characteristics of included studies for further details on who was blinded.

### Follow up and exclusions

#### Drop-outs

The overall number of participants lost to follow up was 894, i.e. 16.08% of the total number of study participants included in the review. Only eight studies specified post randomisation losses and later losses (Asilian 1995; Asilian 2003; Firooz 2005; Firooz 2006; Kochar 2006; Lynen 1992; Momeni 1996; Reithinger 2005).

We have categorised the drop-outs into groups according to the percentage of evaluable participants (Characteristics of included studies).

#### Intention-to-treat analyses

Losses to follow up accounted for 34 studies, and the other 15 reported no drop-outs. However, 28 out of the 34 studies did not carry out intention-to-treat analyses (ITT) or rather they just assessed participants who completed treatment. For each study, we have taken all participants that were randomised into account when introducing the data in our tables. We assumed that missing data were treatment failures. Concerning the losses to follow up, it was not always possible to determine within which arm the losses occurred, and therefore perform ITT analyses. Seven RCTs reported losses without specifying how many belonged to each treatment group (Ben- Salah 1995; Dandashi 2005; Gholami 2000; Momeni 1996; Nilforoushzadeh 2004; Sadeghian 2007; Sharquie 1997).

### Other potential sources of bias

In addition, other 'quality' indicators that may lead to bias but that are not assessed within the risk of bias domain are the following:

#### Sample size calculation declared

Only 13 studies reported a sample size calculation. The studies were further classified into three main groups (small, medium and large) according to their size (see Characteristics of included studies for more details).

#### Inclusion and exclusion criteria defined

For the majority of the studies, the most common reason for excluding a participant from the trial was previous treatment with anti-*Leishmania* therapy prior to entering the trial, as well as suffering from any chronic or concomitant disease (see Characteristics of included studies for more details).

#### Reporting of Leishmania species involved

Twelve studies failed to mention the causative parasite. Eighteen trials mentioned the endemic nature of the parasite in the area and therefore assumed that was the species of parasite causing the development of the disease. Of these, four studies reported that infections in the respective endemic areas were caused by *L. major* and *L. tropica* (Asilian 1995; Iraji 2005; Sharquie 1997; Sharquie 2001), in seven studies *L. major* was presumed to be the causative parasite (Alkhawajah 1997; Faghihi 2003; Firooz 2005; Iraji 2004; Larbi 1995; Lynen 1992; Sadeghian 2006B), and seven studies reported that infections in the area were caused by *L. tropica* (Dogra 1990; Dogra 1991; Dogra 1992; Dogra 1996; Esfandiarpour 2002; Firooz 2006; Özgöztasi 1997) . Eleven studies that checked the origin of the *Leishmania* species reported that CL was caused by *L. major* (Alrajhi 2002; Asilian 2003; Asilian 2006; Gholami 2000; Mohebali 2007; Momeni 1996; Momeni 2002; Nassiri-Kashani 2005; Sadeghian 2006; Ben- Salah 1995; Shazad 2005), six by *L. tropica* (Dandashi 2005; Dogra 1990; Harms 1991; Kochar 2000; Kochar 2006; Reithinger 2005), and only two by both parasites (Momeni 2003; Salmanpour 2001).

#### Time of follow-up period

The follow-up period ranged from three to six weeks in most studies and to one year in two studies (Alrajhi 2002; Faghihi 2003). In two studies (Dandashi 2005; Salmanpour 2006) the length

of follow-up period was not reported. Although the most common follow-up period was one month, five studies (Asilian 2004A; Mohebali 2007; Sadeghian 2006B; Sadeghian 2007; Salmanpour 2001) performed a six month follow-up post treatment period.

#### Baseline comparability of severity of infection, age, sex and duration of complaint

Regarding the baseline characteristics as gender, age, infection severity, and symptom/sign duration, not all studies reported comparability between arms or provided detailed information: six studies did not compare baseline characteristics at all or at least didn't mention if there was comparability among groups (Al-Fouzan 1991; Dandashi 2005; Dogra 1992; Dogra 1990; Dogra 1996; Salmanpour 2006), four trials reported unclear information on comparability, and so it was impossible to ensure the groups comparability (Dogra 1990; Dogra 1991; Nilforoushzadeh 2004; Zerehsaz 1999). Most people enrolled into the RCTS were > 12 years old. In four studies (Asilian 1995; Asilian 2003; Lynen 1992; Özgöztasi 1997) participants were recruited in primary schools. Two studies included one participant as young as three months old (Sharquie 1997), and one ten months old (Zerehsaz 1999). The ages of older participants ranged from 40 (Mashood 2001) to 69 to 75 years old (Kochar 2006; Nilforoushzadeh 2006; Nilforoushzadeh 2007; Zerehsaz 1999), although in one study, not being carried out in primary schools, the oldest participant was 20 years old (Reithinger 2005). Not all the RCTs provided the male/female ratio. However, the overall ratio was 4:3 (2050/1588). Two RCTs included only male participants Mashood 2001; Shazad 2005).

#### Conflict of interest

Thirty-six of the 49 studies failed to mention a potential conflict of interest or any funding for the investigators. The remaining trials were supported by Janssen (Dogra 1990; Dogra 1996; Momeni 1996; Nassiri-Kashani 2005), Pfizer (Alrajhi 2002), Imperial Chemical Industries (Dogra 1991), Behvazan company who supported a trial by providing the ketoconazole and the placebo tablets (Momeni 2003) and finally Thermo surgery Technologies (Reithinger 2005). Six trials were granted by Institutional (academic and/or governmental/WHO) grants (Alkhawajah 1997; Faghihi 2003; Firooz 2005; Firooz 2006; Mohebali 2007; Reithinger 2005).

## Effects of interventions

We did not find always the primary outcome measure we had hoped for when we wrote the protocol. We had defined our primary outcome measure as the percentage of lesions cured at three months after the end of treatment. In some RCTs the unit of analysis was not lesion(s) but participants. Only nine RCTs (Alkhawajah 1997; Asilian 2004B; Asilian 2006; Dandashi 2005; Firooz 2005; Harms 1991; Larbi 1995; Mujtaba 1999; Sharquie 1997) reported the primary outcome as percentage of lesions cured. The rest of the trials reported the percentages in terms of participants.

Of the 49 studies evaluated, only eight RCTs reported the percentage of participants or lesions cured at 3 months follow-up. Two RCTs (Dandashi 2005; Salmanpour 2006) did not report in a clear manner the time of assessment of the primary outcome, and the remaining studies reported a time ranging from just at the end of treatment to six months after treatment.

Secondary outcome measures were reported by speed of healing (time taken to be 'cured') in 7 studies; duration of remission and percentage of people with treated lesions that recur within more than 6 months in 12 studies; prevention of scarring in 8 studies; quality of life in 2 studies (Esfandiarpour 2002; Reithinger 2005); and adverse effects in all of them except 3 (Kochar 2006; Kochar 2006; Nilforoushzadeh 2004). We have described them below and recorded in the Characteristics of included studies. Three studies did not report secondary outcomes (Jaffar 2006; Kochar 2006; Kochar 2006; Nilforoushzadeh 2004). We did not find any RCT where measurements had been made of the degree of functional or aesthetic impairment.

Tertiary outcome measures were reported by microbiological or histopathological cure of skin lesions in 12 studies. We have described them below and recorded in the Characteristics of included studies. We did not find any RCT which evaluated other tertiary outcomes such as change in ability to detect *Leishmania* by parasitological diagnostic methods (e.g. smear, PCR or culture), development of cell-mediated immunity (i.e. positive leishmanin skin test) or emergence of resistance.

Only 13 out of the 49 studies stated a compliance assessment of participants but data was not shown. In only one study (Lynen 1992) was compliance calculated as the total number of applications given in each group divided by the number of days that participants had been under treatment (64.5% and 65.56% were the percentages in the diminazene aceturate (Berenil) and cetrimide and chlorhexidine (Savlon) group respectively).

Only those outcomes with data are described below. If a particular primary, secondary or tertiary outcome is missing, then this is because no suitable data was found.

### 1. Systemic and intralesional antimonials

#### 1.1 Meglumine antimoniate

#### Different doses of intralesional meglumine antimonate

***Primary outcome: Percentage of lesions cured around three months after the end of treatment.***

A RCT (Mujtaba 1999) from Pakistan compared intralesional (IL) meglumine antimoniate (MA) weekly with ILMA fortnightly, until complete cure or up to eight weeks. Two months after treatment, the results showed complete cure of lesions in 92% (102/111) and

85.6% (89/104) in the respective groups. There was no statistical difference between weekly or fortnightly administration of ILMA (RR 1.07; 95% CI 0.98, 1.18 Analysis 1.1).

***Secondary outcomes: Speed of healing***

The majority of lesions had healed at six weeks in both groups with minimal or absent scarring. Authors did not report adverse effects in any of the participants, except transient pain at the site of the injections in both groups.

**Intralesional versus intramuscular administration of meglumine antimonate**

One RCT (Alkhawajah 1997) from Saudi Arabia, compared ILMA every other day with IMMA 6 days a week, over a 30 day period until the lesions had blanched. There was no data to address the primary outcome of percentage of lesions cured around 3 months after the end of treatment, however the authors did report complete cure of lesions in 68.6% (48/70) and 59.7% (46/77) of the respective groups at the end of the treatment period.

***Secondary outcomes: Adverse effects***

Regarding adverse effects, both groups reported pain at the site of injection although it was greater in the ILMA group.

### 1.2 Stibogluconate

**Intralesional versus intramuscular administration of sodium stibogluconate**

***Primary outcome: Percentage of participants with a complete cure around three months after the end of treatment.***

A RCT (Reithinger 2005) from Afghanistan compared IL SSG for up to 29 days with IM SSG daily for 21 days. Two months after treatment, results showed complete cure of participants in 47.3% (70/148) and 18% (26/144) of the IL SSG and IM SSG groups, respectively. Cure rates were significantly higher in the IL SSG group compared with the IM administration group (RR 2.62; 95% CI 1.78, 3.86 Analysis 2.1).

***Secondary outcomes: Speed of healing***

The speed of healing took a median of 75 days for the IL SSG group and 100 days or more for the IM SSG group (the original paper reported that the time to cure was significantly shorter for participants treated with thermotherapy; P = 0.003, by the log-rank test).

***Secondary outcomes: Adverse effects***

Regarding adverse effects, in the IL SSG group one participant reported bradycardia and one an undefined local reaction. In the IM SSG group one participant reported bradycardia, one tachycardia and one palpitation.

## 2. Non-antimonial systemic treatments

### 2.1 Oral antifungals

#### 2.1.1 Ketoconazole

**Different doses of ketoconazole**

A RCT (Alsaleh 1995) from Kuwait compared oral 600 mg/day ketoconazole with oral 800 mg/day ketoconazole, for 6 weeks or until the participant was cured (whichever occurred earlier). There was no data to address the primary outcome of percentage of participants with a complete cure around 3 months after the end of treatment, however the authors did report complete cure of 66.7% (12/18) and 60% (9/15) participants in the respective groups at the end of the treatment period.

***Secondary outcomes: Adverse effects***

None of the participants from either group relapsed during a six month follow-up. With regard to adverse effects, 1 participant had nausea and vomiting in the ketoconazole 800 mg/day group.

**Ketoconazole versus intralesional meglumine antimonate**

A RCT (Salmanpour 2001) from Iran compared oral ketoconazole for 30 days with ILMA, 6 to 8 injections biweekly. There was no data to address the primary outcome of percentage of participants with a complete cure around three months after the end of treatment. However the authors did report that 6 weeks after treatment there was a complete cure of 89% (57/64) and 72% (23/32) of participants in the respective groups.

***Secondary outcomes: Adverse effects***

In the ketoconazole group the most common side effect cited was nausea and abdominal pain, and liver enzymes increased two-fold in two participants returning to normal two weeks after the end of treatment. In the MA group, the most common side effect was redness and swelling after the injection. None of the side effects was significant enough to discontinue treatment.
We also found one trial comparing oral ketoconazole with topical paromomycin/MBCL (Özgöztasi 1997) that is assessed in the topical paromomycin section (3.2).

#### 2.1.2 Itraconazole

**Itraconazole versus placebo**

***Primary outcome: Percentage of participants with a complete cure around three months after the end of treatment.***

A RCT (Nassiri-Kashani 2005) from Iran compared oral itraconazole with placebo for eight weeks. Three months after treatment, results showed complete cure of participants in 67% (67/100) and 53% (53/100) of the respective groups. Cure rates were significantly higher in the oral itraconazole group compared with placebo in *L. major* infections (RR 1.26; 95% CI 1.00, 1.59 Analysis 3.1).
A RCT (Dogra 1996) from India, compared oral itraconazole with placebo for six weeks. Three months after treatment, results showed complete cure of participants in 7/10 (70%) and 1/10 (10% ) of the respective groups. Cure rates were significantly higher in the oral itraconazole group compared with placebo in *L. tropica* infections (RR 7.00; 95% CI 1.04, 46.95 Analysis 3.1).
A RCT (Al-Fouzan 1991) from Kuwait compared oral itraconazole with placebo for six to eight weeks. Two months after treatment, results complete cure of participants in 73% (11/15) and none in the oral intraconazole and placebo groups, respectively. There was no significant differences regarding cure rates between oral itraconazole and placebo in *L. major* and *L. tropica*-infected participants (RR 14.38; 95% CI 0.95, 217.99 Analysis 3.1).
The following two trials did not address the primary outcome of percentage of participants with a complete cure around three months after the end of treatment, however they did report complete cure of participants at other times. A RCT (Momeni 1996) from Iran compared oral itraconazole for three weeks with placebo. Fifty-one days after treatment, results showed complete cure of participants in 51.4% (36/70) and 38.6% (27/70) of the respective groups. A RCT (Dogra 1992) from India compared oral itraconazole for six weeks with placebo. At the end of the treatment period, complete cure of participants occured in 75% (15/20) and 0% (0/20) in the oral itraconazole and placebo groups, respectively.

***Secondary outcomes: Adverse effects***

In one study (Al-Fouzan 1991) two participants from the itraconazole group reported nausea and headache during the course of treatment, and one participant had elevated liver enzymes that returned back to normal upon discontinuation of the drug. Another study (Dogra 1992) reported nausea in 12 cases (30%) in itraconazole and dapsone groups. However, in the itraconazole group, 2 cases (10%) had mild abnormality in liver function that reverted after completion of therapy. In one study (Momeni 1996) six participants in itraconazole group and four participants in the placebo group complained of mild abdominal pain and nausea. No laboratory values were outside normal limits. In another study (Dogra 1996) one participant showed abnormality in liver function and one participant had nausea in the itraconazole group. Participants of the placebo group did not report adverse effects. In one study (Nassiri-Kashani 2005) the most common ones were gastrointestinal complaints and headache reported only in the itraconazole group during the follow-up period. In the placebo group adverse events were reported only during the treatment period.

***Tertiary outcomes: Microbiological or histopathological cure of skin lesions***

In 1 study (Dogra 1996) parasitological cure occurred in 8/10 (80%) of itraconazole-treated participants and none in the placebo group, at 6 weeks follow-up (RR 17.00; 95% CI 1.11, 259.87 Analysis 3.2).

**Itraconazole versus no treatment**

A RCT (Dogra 1990) from India compared oral itraconazole for six weeks with no treatment. There was no data to address the primary outcome of percentage of participants with a complete cure around 3 months after the end of treatment, however the authors did report complete cure of participants in 66.7% (10/15) of the treatment group but none in the no treatment group.

***Secondary outcomes: Remission***

Participants responding to therapy revealed no relapses at three month follow-up.

***Secondary outcomes: Adverse effects***

Regarding adverse effects, the drug was generally well tolerated, although 3/15 participants (20%) reported mild headache and dizziness in the itraconazole group.

***Tertiary outcomes: Microbiological or histopathological cure of skin lesions***

At 6 weeks, 10/15 (66.7%) of the participants in the itraconazole group were free of parasites. Untreated participants were still parasitologically active.

### 2.1.3 Fluconazole

**Fluconazole versus placebo**

***Primary outcome: Percentage of participants with a complete cure around three months after the end of treatment.***

One RCT (Alrajhi 2002) from Saudi Arabia compared oral fluconazole for six weeks with placebo. Three months after treatment, results showed complete cure of participants in 63/106 (59%) and 22/103 (21%) of the oral fluconazole and placebo groups, respectively. Cure rates were significantly higher in the oral fluconazole compared with placebo (RR 2.78; 95% CI 1.86, 4.16 Analysis 4.1).
One RCT (Dandashi 2005) from Aleppo-Syria compared fluconazole for six weeks with placebo. This trial did not address the primary outcome of percentage of lesions cured around 3 months

after the end of treatment and in fact the time period was not reported, however the authors did report a complete cure of lesions in 75/264 (28.4%) and 10/102 (9.8%) of the respective groups.

#### *Secondary outcomes: Speed of healing*

Only 1 study (Alrajhi 2002), reported that the speed of healing took a median of 8.5 and 11.2 weeks in the fluconazole and placebo groups respectively (the original paper reported that the time to cure was significantly shorter for participants treated with thermotherapy; $P < 0.001$, by the log-rank test). Also, none of the participants with complete healing had a relapse during a mean of seven months.

#### *Secondary outcomes: Adverse effects*

In both studies (Alrajhi 2002; Dandashi 2005) participants from reported mild and similar side effects, although the authors did not enumerate them.

### 2.2 Oral dapsone

#### Dapsone versus placebo

A RCT (Dogra 1991) from India compared dapsone tablets for six weeks with placebo. There was no data to address the primary outcome of percentage of participants with a complete cure around 3 months after the end of treatment, however the authors did report complete cure of participants in 82% (49/60) in the dapsone group but none in the placebo group at the end of treatment.
Another RCT from the same author (Dogra1992) compared oral dapsone for six weeks with placebo. There was no data to address the primary outcome of percentage of participants with a complete cure around 3 months after the end of treatment, however the authors did report complete cure of 90% (18/20) of the participants in the oral dapsone group and 0% (0/20) in the placebo group at the end of treatment.
We did not pool the RCTs, performed by the same author, testing the dapsone efficacy in *L. tropica* infections because the data about complete cure of participants was not collected around three months after the end of treatment period.

#### *Secondary outcomes: Remission*

In one study (Dogra 1992) participants initially responding to therapy did not relapse at follow-up, while 2 cases with single lesions (10%) demonstrated spontaneous healing in the placebo group at 3 months follow-up.

#### *Secondary outcomes: Adverse effects*

Regarding adverse effects, nausea was reported in 12 cases (30%) in the dapsone group. In the other study (Dogra1991) 5% (3/60) of cases developed anaemia and 15% (9/60) nausea in the dapsone group.

#### *Tertiary outcomes: Microbiological or histopathological cure of skin lesions*

Regarding the parasitological cure, 5% (3/60) of participants in the placebo group showed healing with negative smears 1 month after treatment (Dogra 1991).

### 2.3 Oral allopurinol

#### Allopurinol versus intramuscular meglumine antimonate

A RCT (Esfandiarpour 2002) from Iran compared oral allopurinol for three weeks, IMMA for two weeks, and oral allopurinol plus MA simultaneously at the same dosage schedule. There was no data to address the primary outcome of percentage of participants with a complete cure around 3 months after the end of treatment, however the authors did report complete cure of participants in 18% (9/50), 24% (12/50) and 46% (23/50), of the respective groups at the end of the treatment period.
Another RCT (Momeni 2002) from Iran, at an army camp compared oral 20 mg/kg/day allopurinol plus low-dose 30 mg/kg/day IMMA for 20 days and 60 mg/kg/day IMMA for 20 days. In this trial too there was no data to address the primary outcome of percentage of participants with a complete cure around 3 months after the end of treatment, however the authors did report 51 days after treatment there was a complete cure of participants in 69% (25/36) and 72% (26/36) of the respective groups.

#### *Secondary outcomes: Adverse effects*

One study (Esfandiarpour 2002) observed a few adverse effects in the allopurinol group: nausea, heartburn (three participants) and mild increase in serum glutamic-oxaloacetic transaminase and serum glutamic pyruvic transaminase levels (two participants). In the other study (Momeni2002) participants tolerated the drugs well and only 17% (6/36) participants in the combined treatment group complained of mild abdominal pain and nausea; however, 3% (1/36) of participants in the IMMA group developed skin eruption and 11% (4/36) of participants suffered generalised muscle pain and weakness.

#### *Tertiary outcomes: Microbiological or histopathological cure of skin lesions*

Only one study (Momeni 2002) reported that 17% (6/36) and 25% (9/36) of participants had parasitologically active lesions 1 month after the end of treatment, respectively.

#### Oral allopurinol versus intravenous sodium stibogluconate

A RCT (Mashood 2001) with participants from the army in Pakistan compared oral allopurinol with IV SSG, for 15 days. There was no data to address the primary outcome of percentage of participants with a complete cure around 3 months after the end of

treatment, however the authors did report at the end of the treatment period, there was a complete cure of participants in 85% (17/20) and 70% (14/20) of the respective groups.

*Secondary outcomes: Adverse effects*

Adverse effects included nausea, vomiting, anorexia or diarrhoea in 1/20 (5%) in the allopurinol group and 4/20 (20%) participants in the SSG group. In the SSG group 2/20 (10%) participants experienced liver abnormalities and 3/20 (15%) of participants myalgia and body aches. In the allopurinol group, liver enzymes were raised in 1/20 (15%) and macular rash in 2/20 (10%) of the participants but there was no myalgia or body aches.

### 2.4 Oral antibiotics

**Oral rifampicin versus placebo**

*Primary outcome: Percentage of participants with a complete cure around three months after the end of treatment.*

A RCT (Jaffar 2006) from Saudi Arabia compared oral rifampicin for four to six weeks with placebo. Three months after treatment, results showed complete cure of participants occured in 45.7% (21/46) and 18.8% (3/16), of the oral rifampicin and placebo groups, respectively. There was no significant differences in cure rates between oral rifampicin and placebo (RR 2.43; 95% CI 0.84, 7.08 Analysis 5.1).

Two RCTs from India did not address the primary outcome of percentage of participants with a complete cure around 3 months after the end of treatment, however 1 trial (Kochar 2000) which compared oral rifampicin for 4 weeks with placebo, reported at the end of the treatment period a complete cure of 68% (17/25) of the participants in the rifampicin group and 4% (1/25) in the placebo groups. The second trial (Kochar 2006) which compared oral rifampicin plus omeprazole for 6 weeks with placebo, reported at the end of the treatment period a complete cure of 64% (16/25) participants in the rifampicin and 12% (3/25) placebo group.

*Secondary outcomes: Adverse effects*

One study (Jaffar 2006) reported that one participant had elevated liver enzymes that returned back to normal upon discontinuation of the drug. Only one study (Kochar 2000) reported that the drug was very well tolerated, and there were no changes in liver function tests or other side effects during therapy.

*Tertiary outcomes: Microbiological or histopathological cure of skin lesions*

One study (Kochar 2000) reported absence of parasites in 8% (2/25) and 32% (8/25) of partially healed lesions from the rifampicin and placebo groups respectively at the end of treatment.

### 2.5 Oral pentoxifylline

**Oral pentoxifylline plus intramuscular meglumine antimonate (IMMA) versus intramuscular meglutamine antimoniate plus placebo.**

*Primary outcome: Percentage of participants with a complete cure around three months after the end of treatment.*

A RCT (Sadeghian 2006) from Iran compared oral pentoxifylline plus IMMA with IMMA plus placebo, for 20 days. Three months after treatment, complete cure of participants occured in 81.3% (26/32) and 50% (16/32) of participants on oral pentoxifylline with IMMA versus IMMA plus placebo, respectively. Cure rates were significantly higher in oral pentoxifylline as an adjuvant compared with IMMA alone (RR 1.63; 95% CI 1.11, 2.39 Analysis 6.1).

*Secondary outcomes: Adverse effects*

Regarding adverse effects, one participant in the IMMA plus placebo group had an allergic maculo-papular itchy rash.

### 2.6 Oral miltefosine

**Oral miltefosine versus intramuscular meglumine antimonate**

*Primary outcome: Percentage of participants with a complete cure around three months after the end of treatment.*

A RCT (Mohebali 2007) performed in Iran compared oral miltefosine for 28 days with IMMA for 14 days. Three months after treatment, results showed complete cure of participants in 26/32 (81.3%) and 25/31 (80.6%) of the oral miltefosine and IMMA groups, respectively. There was no significant difference in cure rates between oral miltefosine and IMMA (RR 1.01; 95% CI 0.79, 1.28 Analysis 7.1).

*Secondary outcomes: Adverse effects*

Participants did not relapse at six months post-treatment. With regard to adverse effects, during the first week participants from the miltefosine-treated group suffered from nausea, vomiting, diarrhoea, abdominal pain and cough. Only participants from the MA-treated group had diarrhoea and local pain. During the second week participants from the miltefosine-treated group suffered from nausea, vomiting, abdominal pain and headache itch, fever. Participants from the MA-treated group developed the same adverse effects and also, local and chest pain, and cough.

### 2.7 Oral zinc sulphate

**Different doses of oral zinc sulphate**

A RCT (Sharquie 2001) from Iraq compared different doses in a day of oral zinc sulphate with no treatment. There was no data to address the primary outcome of percentage of participants with a complete cure around 3 months after the end of treatment, however the authors did report that 45 days after treatment, there was complete cure of participants in 66.7% (26/39), 73% (27/37), 79% (31/39) of the 2.5, 5 and 10 mg/kg/day zinc sulphate groups, respectively. However, all lesions in the control group were active at day 45, and thus none of the participants were cured.

***Secondary outcomes: Speed of healing***

In the zinc sulphate 2.5 mg/kg group, the mean time taken to cure was 30.8 days (21 to 45): 29.96 days (15 to 45) in the 10 mg/kg group and 28.32 days (15 to 45) in the 10 mg/kg (the original paper reported that the time to cure was not statistically significant between the different treatment groups). None of the participants recovered in the control group.

***Secondary outcomes: Prevention of scarring***

In all treatment groups there was minimal or no scarring at the site of lesions.

***Secondary outcomes: Adverse effects***

Regarding adverse effects, 1 participant each in the 2.5 mg/kg and 5 mg/kg groups and 5 in the 10 mg/kg group had nausea and vomiting. Only 1 participant from the 5 mg/kg group had a leishmanid reaction, and 2 participants in the 2 and 5 mg/kg groups and 1 in the 10 mg/kg, had oedema.

## 3. Non-antimonial topical or intralesional therapies

### 3.1 Topical antifungals

**Topical 2% miconazole versus topical 1% clotrimazole**

A RCT (Larbi 1995) from Saudi Arabia compared miconazole cream with clotrimazole cream for 30 days.This trial did not address the primary outcome of percentage of lesions cured around 3 months after the end of treatment period, however the authors did report there was no cure of lesions in the miconazole group and15% (14/89) cure of lesions in the clotrimazole group.

***Secondary outcomes: Adverse effects***

In both treatment groups, the medication was well-tolerated and no side effects were observed.

**Ketoconazole cream versus placebo**

A RCT (Momeni 2003) from Iran compared topical ketoconazole with placebo, twice daily for 21 days. This trial did not address the primary outcome of percentage of participants cured around 3 months after the end of the treatment period, however the authors did report that 51 days after treatment there was a complete cure of participants in 24% (11/45) and 13% (6/45) of the ketoconazole and placebo groups respectively.

***Secondary outcomes: Adverse effects***

One month after completion of treatment, 60% (27/45) and 64% (29/45) of participants still had active lesions in the ketoconazole and in the placebo groups respectively. Regarding adverse effects, the drugs were well tolerated and only two participants (group unknown) complained of mild pruritus at the site of the lesions.

### 3.2 Topical paromomycin (aminosidine)

**Paromomycin versus placebo**

***Primary outcome: Percentage of participants with a complete cure around three months after the end of treatment.***

A RCT (Asilian 1995) from Iran compared 15% paromomycin and 10% urea (PR-U) with placebo, twice a day for 14 days. Two and a half months after treatment, complete cure of participants occured in 63.5% (80/126) and 63.2% (79/125) of those on PR-U and placebo respectively .

A RCT (Ben- Salah 1995) from Tunisia compared PR-U in soft white paraffin with placebo, twice per day for 14 days. Two and a half months after treatment (day 105), complete cure of participants occured in 60.6 % (40/66) of both groups.

A pooled analysis of these 2 trials showed that differences in cure rates between topical PR-U and placebo were not statistically significant (RR of 1.00; 95% CI 0.86, 1.17 Analysis 8.1).

***Primary outcome: Percentage of lesions cured around three months after the end of treatment.***

A RCT (Asilian 2006) from Iran compared topical 15 % paromomycin sulphate in 12% MBCL (PR-MBCL) with placebo, twice daily for 30 days. Two months after treatment, complete cure of lesions occured in 41.2% (14/34) and 13.3% (4/30 lesions) of the PR-MBCL and placebo groups, respectively. Cure rates were significantly higher in the topical PR-MBCL group compared with placebo (RR 3.09; 95% CI 1.14, 8.37 Analysis 9.1).

A RCT (Iraji 2005) from Iran compared PR-U with placebo, applied topically on each lesion twice daily for 30 days. The primary outcome of percentage of lesions cured 3 months after the end of treatment was not addressed but they did report complete cure of participants in 12.5% (5/40) and 17.5% (7/40) of the respective groups, 1 month after treatment.

***Secondary outcomes: Prevention of scarring***

Only 1 study (Asilian 2006) reported that at the end of the study, there was no significant difference in number of deep or disfiguring scars between the PR-MBCL and placebo groups (RR 2.35; 95% CI 0.69, 8.07 Analysis 9.2). It should be noted however that we have used the number of lesions originally randomised in presenting the data in this analysis, whereas in the original paper the authors assessed scarring only in those lesions that were completely improved at the end of the study (which perhaps makes more sense as a denominator). Both methods of calculating the degree of scarring failed to show any statistically significant differences.

***Secondary outcomes: Adverse effects***

Regarding adverse effects, 12 participants between the 2 groups reported a local reaction (inflammation, vesiculation, pain or redness or both) (Ben- Salah 1995); 8 participants from the PR-U-treated group and 11 from the placebo group complained about redness, local pain, vesiculation and inflammation (Asilian 1995); 3 cases in the PR-U group reported mild contact dermatitis (Iraji 2005); and mild and tolerable itch, burning, redness, discharge, oedema and pain, in all 3 groups (Asilian 2006).

***Tertiary outcomes: Microbiological or histopathological cure of skin lesions***

In a study (Asilian1995), there was no significant difference in the number of negative parasitologic smears at day 105 between PR-MBCL and placebo groups (RR 1.09; 95% CI 0.98, 1.22 Analysis 8.2). In another study (Asilian2006), PR-MBCL group 64.7% (22/34) and placebo group 20% (6/30) were parasitologically free 2 months after the end of treatment (RR 3.24; 95% CI 1.52, 6.90 Analysis 9.3).

**Paromomycin combined with urea versus intralesional meglumine antimonate**

A RCT (Faghihi 2003) from Iran compared PR-U ointment, twice per day, for a mean duration of 45 days and a maximum duration of 3 months with ILMA weekly. There was no data to address the primary outcome of percentage of participants with a complete cure around 3 months after the end of treatment, however at less than 2 months after treatment, the authors reported complete cure of participants in 16.6% (8/48) and 41.7% (20/48) of the PR-U and ILMA groups, respectively.

Another RCT (Shazad 2005) from Iran compared topical PR-U ointment twice a day for 20 days with ILMA (dose unspecified) every other day for 20 days. This trial did not address the primary outcome of percentage of participants cured around 3 months after the end of the treatment period, however 1 week after end of treatment the authors reported complete cure of participants in 20/30 (66.7%) and 18/30 (60%) of the respective groups.

***Secondary outcomes: Remission***

One study (Faghihi 2003) reported after one year a reactivation after complete recovery in 6.3% (3/48) of the participants due to lymphatic spread in the PR-U group. In the MA group recurrence occured after complete recovery in 6.3% (3/48) of participants due to non lymphatic spread. Scarring occured in 4.2% (2/48) of participants in the PR-U group and for 8.3% (4/48) in the MA group. They did not observe any residual scar or relapse after one year.

***Secondary outcomes: Adverse effects***

Regarding adverse effects, one study (Shazad 2005) reported that 1/30 in the PR-U group and 3/30 participants in the MA treatment group withdrew from the study because of cutaneous reactions like erythematosus, urticaria or lymphadenitis with pain. They were all put on systemic MA and cured thereafter. They did not observe any systemic toxic reaction attributable to the drug.

**Paromomycin combined with MBCL versus oral ketoconazole**

A RCT (Özgöztasi 1997) from Turkey compared topical PR-MBCL twice per day for 15 days with oral ketoconazole for 30 days. This trial did not address the primary outcome of percentage of participants cured around 3 months after the end of the treatment period, however 1 month after the end of treatment the authors reported complete cure of participants in 37.5% (15/40) of the paromomycin group and none in the ketoconazole group.

***Secondary outcomes: Adverse effects***

Irritant contact dermatitis was the most common side effect described in the PR-MBCL group. In contrast, the ketoconazole-treated participants reported no adverse effects.

***Tertiary outcomes: Microbiological or histopathological cure of skin lesions***

The PR-MBCL and the ketoconazole groups showed incomplete improvement (absence of parasites on culture or smear) in 20% (8/40) and 21.9% (7/32) of participants respectively at 4 weeks post-treatment.

**Paromomycin combined with MBCL versus topical photodynamic therapy (PDT)**

***Primary outcome: Percentage of lesions cured around three months after the end of treatment.***

In a RCT (Asilian 2006) from Iran compared topical PR-MBCL applied topically twice daily for 28 days with topical PDT every week for 4 weeks. Two months after treatment, results showed complete cure of lesions in 41.2% (14/34) and 93.5% (29/31) of the PR-MBCL and PDT groups respectively. Cure rates were

significantly higher in the PDT group compared with topical PR-MBCL (RR 0.44; 95% CI 0.29, 0.66 Analysis 10.1).

***Secondary outcomes: Prevention of scarring***

At the end of the study, there was no significant difference in number of deep or disfiguring scars between paromomycin and PDT groups (RR 15.54; 95% CI 0.93, 258.58 Analysis 10.2). Both groups had mild and tolerable itch, burning, redness, discharge, oedema and pain as adverse effects.

***Tertiary outcomes: Microbiological or histopathological cure of skin lesions***

Two months after the end of treatment, PR-MBCL group 64.7% (22/34 lesions) were parasitologically free as were 100% (31/31) of the PDT group (RR 0.65; 95% CI 0.51, 0.84 Analysis 10.3).

**Different regimens of topical paromomycin**

***Primary outcome: Percentage of participants with a complete cure around three months after the end of treatment.***

A RCT (Asilian 2003) from Iran compared 2 tubes of 15 g of paromomycin ointment (each tube was enough for 2 applications per day for 14 days) for a 4 week treatment with 1 tube of 15g of paromomycin ointment for 2 weeks plus placebo ointment for 2 weeks more. Two and a half months after treatment, results showed complete cure of participants in 50% (58/117) and 37% (43/116) of the 4 week and 2 week regimens, respectively. There was no significant differences in cure rates between the 4 week and the 2 week treatment (RR 1.34; 95% CI 0.99, 1.80 Analysis 11.1).

***Secondary outcomes: Adverse effects***

Participants tolerated well the treatment and they did not observe any adverse effect or adverse reactions to the ointment in either group.

***Tertiary outcomes: Microbiological or histopathological cure of skin lesions***

Three months (day 105) after treatment initiation, there was no significant differences in parasitological cure between paromomycin for 4 weeks and 2 weeks (RR 1.47; 95% CI 1.03, 2.11 Analysis 11.2).

### 3.3 Intralesional zinc sulphate

**Intralesional zinc sulphate versus intralesional sodium stibogluconate versus intralesional hypertonic sodium chloride solution (HSCS)**

A RCT (Sharquie 1997) from Iraq compared mono doses of IL zinc sulphate solution, IL SSG and IL HSCS. A few lesions on unimportant and unexposed parts of the body were left as controls. The primary outcome of percentage of lesions cured 3 months after the end of treatment was not addressed but the authors did report 6 weeks after treatment, complete cure of lesions in 94.8% (36/38), 88.5% (31/35) and 85% (34/40) of the respective groups. In the untreated group, 9 participants with 38 lesions were followed up for 6 weeks and they had no decrease in the size of the lesions and parasites could still be detected at the end of the study.

***Secondary outcomes: Speed of healing***

In the zinc sulphate group most lesions were cured by 30 days. In the HSCS and in the SSG group, lesions were cured after 30 days.

***Secondary outcomes: Prevention of scarring***

In all three groups the scar was minimal or absent after healing but all participants developed postinflammatory hyperpigmentation. In the control group, some lesions (mainly on the lower limbs) showed signs of infection.

***Secondary outcomes: Adverse effects***

Regarding adverse effects, all participants from the three groups except the group control, had pain at the time of the injection.

**Intralesional zinc sulphate versus intralesional meglumine antimonate**

One RCT (Iraji 2004) from Iran compared IL zinc sulphate with ILMA. In cases with slight to mild improvement, the authors gave another injection after two weeks. This trial did not address the primary outcome of percentage of participants cured around 3 months after the end of the treatment period, however the authors did report at the end of the treatment period, complete cure of participants in 53% (26/49) and 38% (21/55) of the respective groups.

A RCT (Firooz 2005) from Iran compared up to six weekly IL zinc sulphate with up to six weekly ILMA. The primary outcome of percentage of lesions cured 3 months after the end of treatment was not addressed but the authors did report 5 weeks after treatment complete cure of lesions in 22.6% (12/53) and 50.9% (27/53) of the respective groups. It is worth pointing out that when looking at baseline characteristics, both mean diameter induration and mean diameter ulceration was higher in the zinc sulphate group (induration: 10.0  11.4 mm, and ulceration: 2.7  4.6 mm) than in the MA group (induration: 2.4  8.7 mm, and ulceration: 0.6  3.6 mm). However, the authors claimed that there was no significant difference between the 2 groups (P > 0.05).

***Secondary outcomes: Adverse effects***

In one study (Firooz 2005), the most commonly observed adverse effect was pain found in 25% (18/72) of participants and by groups was: 13/36 (36.1%) and 13.9% (5/36) in the zinc sulphate

and MA groups, respectively. Participants from the zinc sulphate group (3/36 cases [8.4%]) complained about burning at the site of injection. Itching occurred in 3/36 cases (8.4%) in the zinc sulphate group and in 9/36 cases (25%) in the MA group. Inflammation occurred in 7/36 cases (19.4%) in the zinc sulphate group and 8/36 cases (22.2%) in the MA group. In the other study ( Iraji 2004), ILMA caused pruritus, erythema and scaling in the periphery of the injection site in three cases. IL zinc sulphate was painful and caused vasovagal shock in two cases due to severe pain.

### 3.4 Topical imiquimod

#### Imiquimod cream versus intramuscular meglumine antimonate

***Primary outcome: Percentage of participants with a complete cure around three months after the end of treatment.***

A RCT (Firooz 2006) from Iran compared 5% imiquimod cream 3 times per week for 28 days plus IMMA for 14 days, with placebo plus IMMA at the same dose. At 3.5 months after treatment, results showed complete cure of participants occured in 26/59 (44.1%) and 24/60 (40%) of treatment and placebo groups, respectively. There was no significant differences in cure rates between the combination of imiquimod plus IMMA and IMMA alone (RR 1.10; 95% CI 0.72, 1.68 Analysis 12.1).

***Secondary outcomes: Remission***

At 4 months after treatment in the participants available for assessment, 1 of 32 participants treated with imiquimod + MA and 3 of 37 participants treated with placebo + MA relapsed.

***Secondary outcomes: Adverse effects***

The only adverse effects related to topical treatment were moderate itch and burning sensation in three imiquimod-treated participants.

### 3.5 Intralesional Hypertonic sodium chloride (HSCS)

#### Intralesional 7% HSCS versus intralesional sodium stibogluconate

A RCT (Sharquie 1997) from Iraq compared mono doses of IL HSCS with IL SSG. The primary outcome of percentage of lesions cured 3 months after the end of treatment was not addressed but the authors did report 6 weeks after treatment, complete cure of lesions in 85% (34/40) and 88.5% (31/35) in the HSCS and SSG groups respectively.

***Secondary outcomes: Speed of healing***

In the HSCS and in the SSG group, lesions were cured after 30 days.

***Secondary outcomes: Prevention of scarring***

In both groups the scar was minimal or absent after healing but all participants developed post-inflammatory hyperpigmentation.

***Secondary outcomes: Adverse effects***

Regarding adverse effects, all participants from both groups had pain at the time of the injection.

#### Intralesional 5% HSCS versus intralesional meglumine antimonate

A RCT (Sadeghian 2006B) from Iran compared IL HSCS with ILMA for six to ten weeks. The primary outcome of percentage of lesions cured 3 months after the end of treatment was not addressed but the authors did report complete cure of lesions in 25% (9/36) and 33.3% (12/36) of the respective groups at the end of the treatment session.

***Secondary outcomes: Adverse effects***

In the HSCS group, three cases of sporotrichoid dissemination were observed but with no allergic reactions. In the MA group, three cases of sporotrichoid dissemination were observed, two satellite lesions and two allergic reactions as redness, oedema and severe itch around the lesions.

### 3.6 Intralesional interferon-gamma (IFN-$\gamma$)

#### Intralesional IFN- $\gamma$ versus intralesional meglumine antimonate

A RCT (Harms 1991) from Syria compared IL IFN -$\gamma$ and ILMA once weekly for five weeks. The primary outcome of percentage of lesions cured 3 months after the end of treatment was not addressed but the authors did report 1 month after treatment complete cure of lesions in 3% (1/37) and 76% (29/38) of the respective groups.

***Secondary outcomes: Adverse effects***

Pain at the injection site of IFN-$\gamma$ was mild on 68 occasions, moderate on 47 and caused severe pain on 38. In the MA group it was mild on 55 occasions, moderate on 51 and severe on 40. Other side effects observed were local maculopapular erythema in the MA group and headache in the IFN -$\gamma$ group.

***Tertiary outcomes: Microbiological or histopathological cure of skin lesions***

Parasitological assessment one month after the end of treatment showed parasite-free lesions in 65% (24/37) and 100% (38/38) in the IFN-$\gamma$ and MA groups respectively.

### 3.7 Topical photodynamic therapy (PDT)

#### Topical PDT versus placebo

***Primary outcome: Percentage of lesions cured around three months after the end of treatment.***

A RCT (Asilian 2006) from Iran compared topical PDT every week for 4 weeks with placebo topically twice daily also for 28 days. Two months after treatment, results showed complete cure of lesions in 93.5% (29/31) and 13.3% (4/30) of the PDT and placebo groups, respectively. Cure rates were significantly higher in the PDT group compared with placebo (RR 7.02; 95% CI 2.80, 17.55 Analysis 13.1).

***Secondary outcomes: Prevention of scarring***

At the end of the study, none of the lesions had deep or disfiguring scars in the PDT group. However, 20% (3/30) of the lesions in the placebo groups had deep or disfiguring scars (RR 0.14; 95% CI 0.01, 2.57 Analysis 13.2). Both groups had mild and tolerable itch, burning, redness, discharge, oedema and pain as adverse effects.

***Tertiary outcomes: Microbiological or histopathological cure of skin lesions***

Two months after treatment, parasitological cure rates were significantly higher in the PDT group (100% (31/31 lesions)) compared to placebo (20% (6/30)) (RR 4.69; 95% CI 2.37, 9.31 Analysis 13.3).

The same author also compared PDT with topical paromomycin plus MBCL which is analysed in section 3.3.

## 4. Measures for promoting healing

#### Topical diminazene aceturate (Berenil) versus topical cetrimide and chlorhexidine (Savlon)

A RCT (Lynen 1992) from Sudan compared diminazene aceturate solution with cetrimide plus chlorhexidine solution for 50 days. This trial did not address the primary outcome of percentage of participants cured around 3 months after the end of the treatment period, however the authors did report complete cure of participants of 80% (28/35) and 57% (20/35) in the respective groups at the end of the treatment period.

#### Secondary outcomes: Remission

In the Berenil group 3 re-ulcerations occurred (2 after 20 days and 1 after 25 days of cure). In the Savlon group, 2 re-ulcerations occurred after 35 days of cure.

#### Secondary outcomes: Adverse effects

Extreme drying of ulcers and surrounding skin occurred in participants in the Berenil group. Participants from the Savlon group experienced a slight burning sensation and drying of the skin at the site of treatment.

## 5. Physical therapies

### 5.1 Laser

#### $CO_2$ laser versus intramuscular meglumine antimonate

A RCT (Asilian 2004B) from Iran compared $CO_2$ laser applied to the lesion with IMMA for 15 days (this treatment was repeated after 15 days of rest). The primary outcome of percentage of lesions cured 3 months after the end of treatment was not addressed but the authors did report 6 weeks after treatment complete cure of lesions in 20/183 (11%) and 30/250 (12%) of the respective groups.

***Secondary outcomes: Speed of healing***

The time taken to be cured was one month for the $CO_2$ laser group and three months for the MA group.

***Secondary outcomes: Prevention of scarring***

In the laser group, most of the scars were acceptable as stated by trialists, except in 5 cases (4%) in which the lesions were located on the joints or neck and the resulting scars raised and were hypertrophic.

***Secondary outcomes: Adverse effects***

Regarding adverse effects, in the laser group complications accounted for 4/123 participants and included hyperpigmentation, persistent redness and 5 participants had hypertrophic scarring. In the MA group 22/110 participants reported myalgia, sensitivity, headache, urticaria and nausea.

### 5.2 Trichloroacetic acid

#### Trichloroacetic acid versus intralesional meglumine antimonate

A RCT (Nilforoushzadeh 2006) from Iran compared trichloroacetic acid (TCA) applied every two weeks until complete re-epithelialization or up to three times, with ILMA weekly until complete re-epithelialization of the lesions or up to six weeks. This trial did not address the primary outcome of percentage of participants cured around 3 months after the end of the treatment period, however the authors did report at the end of the treatment period a complete cure of participants in 26/40 (65%) and 23/40 (57.5%) of the respective groups.

***Secondary outcomes: Remission***

There were 5/40 (12.5%) cases of recurrence in TCA groups and 4/40 (10%) in MA after 3 months follow-up.

***Secondary outcomes: Adverse effects***

The observed adverse effects included mild erythema and itch (two cases in MA group).

***Tertiary outcomes: Microbiological or histopathological cure of skin lesions***

Parasitologic tests were positive at week 6 in 11/40 (27.5%) and 10/40 (25%) in the TCA and MA groups, respectively.

### 5.3 Cryotherapy

**Cryotherapy alone versus intralesional meglumine antimonate with cryotherapy versus intralesional meglumine antimonate monotherapy**

A RCT (Asilian 2004A) from Iran compared cryotherapy plus ILMA, cryotherapy and ILMA alone. The primary outcome of percentage of lesions cured 3 months after the end of treatment was not addressed but the authors did report at the end of the treatment period a complete cure of lesions in 80.5% (120/149), 52.2% (120/230) and 52.5% (84/160) of the respective groups . A RCT (Salmanpour 2006) from Iran compared a combination of cryotherapy and ILMA with cryotherapy alone and ILMA monotherapy. This trial did not address the primary outcome of percentage of participants cured around 3 months after the end of the treatment period, however the authors did report complete cure of participants in (18/20) 89%, (14/20) 67.8% and (15/20) 75%, of the respective groups, although they did not report the time of this assessment.

***Secondary outcomes: Speed of healing***

Only one study (Asilian 2004A) reported that none of the cured lesions recurred during the six month follow-up period.

***Secondary outcomes: Adverse effects***

Asilian 2004A reported mild adverse side-effects, such as post-inflammatory hypopigmentation: 5/100 of cases in the combined cryotherapy and ILMA group and 10/200 in the cryotherapy group. In the other study (Salmanpour 2006) there were no serious side-effects in any of the treatment groups. However, 33%, 28% and 19% in combination of cryotherapy and MA, cryotherapy alone and MA alone groups, respectively reported erythema and edema of the lesions and perilesional area.

***Tertiary outcomes: Microbiological or histopathological cure of skin lesions***

Only one study (Asilian 2004A) reported that all cured lesions showed negative direct smears at the end of treatment and six weeks after treatment.

**Triple combination of cryotherapy plus 15% paromomycin plus intralesional meglumine antimonate versus intralesional meglumine antimonate monotherapy**

A RCT (Nilforoushzadeh 2004) from Iran compared a combined triple therapy of cryotherapy, paromomycin cream plus ILMA with ILMA monotherapy. This trial did not address the primary outcome of percentage of participants cured around 3 months after the end of the treatment period, however the authors did report 6 weeks after treatment complete cure of participants in 68/81 (89.5%) and 57/76 (70.4%) of the respective groups.

### 5.4 Thermotherapy

**Thermotherapy using radiofrequency waves versus intralesional meglumine antimonate**

***Primary outcome: Percentage of participants with a complete cure around three months after the end of treatment.***

A RCT (Sadeghian 2007) from Iran compared controlled localized heating using a radiofrequency heat generator and ILMA for four consecutive weeks. Six months after treatment, results showed complete cure of participants in 80.7% (46/57) and 56.7% (34/60) of the heating and ILMA group, respectively. Heat was more efficacious than ILMA. With regard to the lesions, complete cure occured in 80.72% (67/83) and 55.32% (52/94) of the thermotherapy and ILMA groups, respectively. Cure rates were significantly higher in the thermotherapy group compared with ILMA both in terms of participants (RR 1.42; 95% CI 1.10, 1.84 Analysis 14.1) and lesions (RR 1.46; 95% CI 1.18, 1.80 Analysis 14.1).

***Secondary outcomes: Remission***

There was no relapse from lesions with complete response in both groups after six months of follow-up.

***Secondary outcomes: Prevention of scarring***

They reported that although all participants with complete response in both groups had scars, the size of the scars was smaller in the heat-treated group (15.9 mm before and 11.2 mm after treatment) than in the MA-treated group (15.0 mm before and 14.8 mm after treatment).

***Secondary outcomes: Adverse effects***

Regarding adverse effects, four participants with ten lesions as well as four cases with sporotrichoid lesions and three cases with

satellite lesions after treatment, developed allergic reactions such as erythema, oedema and pruritus around the lesions in the heat-treated group. There was only one case with satellite lesions after treatment in the MA group.

#### Thermotherapy using radiofrequency waves versus intralesional or intramuscular sodium stibogluconate

***Primary outcome: Percentage of participants with a complete cure around three months after the end of treatment.***

A RCT (Reithinger 2005) from Afghanistan compared IL SSG for up to 29 days, IM SSG daily for 21 days, and thermotherapy using radiofrequency waves. Two months after treatment, results showed that complete cure of participants accounted for 47.3% (70/148), 18% (26/144) and 54% (75/139), respectively. Cure rates were significantly higher in the thermotherapy group compared with IM SSG (RR 2.99; 95% CI 2.04, 4.37 Analysis 15.1) but there was no significant difference compared with IL SSG (RR 1.14; 95% CI 0.91, 1.43 Analysis 15.1).

***Secondary outcomes: Speed of healing***

The speed of healing took a median of 75 days for the IL SSG group, 100 days or more for the IM SSG group and a median of 53 days for the thermotherapy group (the original paper reported that the time to cure was significantly shorter for participants treated with thermotherapy; P = 0.003, by the log-rank test).

***Secondary outcomes: Adverse effects***

One participant reported bradycardia and one an undefined local reaction in the IL SSG group. In the IM SSG group, one participant reported bradycardia, one tachycardia and one palpitation. In the thermotherapy some participants experienced superficial second degree burns.

### 6. Alternative therapies

#### Topical garlic cream versus placebo

A RCT (Gholami 2000) from Iran compared 5% garlic cream treatment with placebo for 3 weeks. This trial did not address the primary outcome of percentage of participants cured around 3 months after the end of the treatment period, however 40 days after treatment the authors reported complete cure of participants in 18/96 (18.75%) and 15/75 (20%) of the respective groups.

#### Topical herbal extract versus intramuscular meglumine antimonate

A RCT (Zerehsaz 1999) from Iran compared topical herbal extract Z-HE plus placebo with IMMA plus placebo. This trial did not address the primary outcome of percentage of participants cured around 3 months after the end of the treatment period, however 6 weeks after treatment, results showed that complete cure of participants in 74.4% (64/86) and 27.1% (23/85) of the respective groups.

**Secondary outcomes: Adverse effects**

Participants in the MA group reported urticaria and generalised itch.

#### Topical honey plus IL meglumine antimonate versus intralesional meglumine antimonate monotherapy

**Primary outcome: Percentage of participants with a complete cure around three months after the end of treatment.**

A RCT (Nilforoushzadeh 2007) from Iran compared topical honey soaked gauze and ILMA with ILMA. Results showed that 2.5 to 3 months after treatment, complete healing occurred in 46% (23/50) and 64% (32/50) of the participants in the respective groups. There was no significant difference in cure rates between topical honey as and adjuvant to ILMA compared with ILMA monotherapy (RR 0.72; 95% CI 0.50, 1.04 Analysis 16.1).

**Secondary outcomes: Speed of healing**

The mean time taken to be cured after omitting drop-outs was 7.04 and 6.3 weeks in the honey plus MA and MA groups respectively.

### Results from the MEDLINE search for adverse effects

A MEDLINE search was made for adverse or side effects combined with therapeutic terms. However, we could only find general papers reporting known adverse effects derived from the evaluated drugs that are already mentioned in the background under the " Description of the intervention" section.

## DISCUSSION

### Summary of main results

The RCTs included in this review have assessed a broad range of treatments and many different clinical questions. Yet they resulted in limited opportunities to describe and pool useful data. We have some concerns regarding the precision of data reported in several studies. Furthermore, because the majority of RCTs had a high risk of bias, it was difficult to conclude whether one treatment was more beneficial than the comparator much of the time. Many interventions discarded as ineffective in an essentially inconclusive study, could still prove to have some benefit if they were evaluated in an adequately powered study. Nonetheless, this review accurately documents the existing RCT evidence on the usefulness

of treatments and that relevant information can be extracted for practice and future research.

We found 49 RCTs that covered at least 19 different interventions, which could be broadly categorised into 6 main groups: antimonial drugs, non-antimonial systemic treatments, topical and IL treatments, promoting healing methods, physical therapies and alternative therapies. Given that sample size per se is not a source of potential bias but a source of potential imprecision that may lead to bias, care has to be exercised in not concluding that the evaluation of the efficacy of interventions of small-sized RCTs was untrustworthy.

It was difficult to evaluate the efficacy of any of the multiple current IL or IM antimony regimens in the absence of any placebo-controlled trials. Limited statistical pooling was possible only for topical 15% paromomycin plus 10% urea for 2 weeks *versus* placebo after considerable data transformation.

There was reasonable RCT evidence in *L. major* infections that the following treatments are better than placebo:

- Oral fluconazole 200 mg/day for 6 weeks
- Topical 15% paromomycin + 12% MBCL twice daily for 28 days
- Photodynamic therapy (PDT) weekly for four weeks

There was reasonable RCT evidence in *L. major* infections that:

- Oral pentoxifylline is a good adjuvant therapy to IMMA
- IL zinc sulphate weekly up to six weeks is ineffective *versus* ILMA
- PDT weekly for 4 weeks is more efficacious than topical 15% paromomycin +12% MBCL twice daily for 28 days

There was reasonable RCT evidence in *L. tropica* infections that itraconazole 200 mg/day for 6 weeks is better than placebo.

There was reasonable RCT evidence in *L. tropica* infections that:

- IL SSG is more efficacious than IM administration
- Thermotherapy is more efficacious than IM SSG

There was reasonable RCT evidence that heat is more efficacious than IMMA administered once a week for four weeks, although the species of *Leishmania* was not reported, in a trial from Iran.

There was insufficient evidence to support the use of:

- ILMA weekly or fortnightly in unreported species
- Itraconazole 200 mg/d for 6 to 8 weeks in *L. major* or mixed (both species together) infections
- Oral rifampicin 10 mg/kg/d twice daily for 4 to 6 weeks *versus* placebo in unreported species
- Oral miltefosine for 28 days versus IMMA for 14 days in *L. major* infections
- Topical 15% paromomycin + 12% MBCL twice daily for 14 days in *L. major* infections
- 4 week *versus* 2 week paromomycin in *L. major* infections
- Topical 5% imiquimod cream 3 times a week as an adjuvant therapy to IMMA in *L. tropica* infections
- Thermotherapy versus IL SSG in *L. tropica* infections
- Topical honey for a maximum of six weeks as an adjuvant therapy to ILMA in unreported species

There was complete absence of RCT evidence on surgery, oral omeprazole alone, IM pentamidine and topical amphotericin B in OWCL.

Although the rest of the studies did report cure, they were not statistically assessed because they were characterised by too short-term an assessment of the primary outcome, or rather they did not report cure rates in our pre-specified time period for the primary outcome. Thus, there was insufficient RCT evidence to make recommendations on local or systemic administration of MA, oral allopurinol alone or in combination with antimonials, oral ketoconazole, oral dapsone, topical antifungals, IL zinc sulphate or IL hypertonic solution, IL IFN-$\gamma$, physical therapies such as $CO_2$ laser, TCA, and cryotherapy, and finally alternative therapies such as garlic cream or topical herbal extract.

## Overall completeness and applicability of evidence

Not all the trials provided the same information regarding the primary, secondary and tertiary outcome measures evaluated for this review. The majority of RCTs did not report the percentage of lesions cured at three months follow-up as a primary outcome and the timing ranged from the end of treatment to six months after treatment. Most of them reported the percentage in terms of participants instead of lesions. However, we now recognise it might have been better to deal with participants rather than numbers of lesions because a few individuals with lots of lesions can skew the data. Lesions cured did not give us a reliable approach of how many participants were completely cured or rather, whether all their lesions had healed. In addition, from a clinical perspective, it may be more relevant to know whether a patient is completely or partially cured irrespective of how many lesions were fully healed by the tested drug. Thus, we will modify the unit of analysis in the update to this review.

The main secondary outcome reported in these studies was the description of adverse events. Several RCTs also reported other secondary outcomes but none reported the degree of functional and aesthetic impairment. The only tertiary outcome reported was "microbiological or histopathological cure of skin lesions".

Although there is a lack of clinical data on CL due to *L. aethiopica*, infections by this parasite appear to be relatively insensitive to antimonial compounds. There are some reports of the clinical effectiveness during follow-up periods of 2 to 21 months with aminosidine sulphate (Paromomycin) (Teklemariam 1994), and high dose intravenous sodium stibogluconate (Chulay 1983). However, we did not find any RCTs related to *L. aethiopica* infections.

Overall, considerable numbers of participants withdrew or were lost to follow up. The majority of trial authors stated that they have performed a compliance assessment but results were seldom shown in the assessed studies. Acquired resistance to anti-*Leishmania* drugs has been studied in the laboratory for several decades, but it is only recently that clinical resistance has been demonstrated. The monitoring of resistance is problematic due at present to an inadequate correlation between clinical and *in vitro* resistance and a lack of knowledge about the molecular and biochemical mechanisms of resistance (Croft 2006).

### Quality of the evidence

Adequate randomisation was reported in 35% (17/49) of the included studies. Only 14% (7/49) had an adequate reporting of allocation concealment. Double-blinding was found in 45% (22/49) of the studies. There was inadequate description of baseline characteristics in 12% (6/49) of the studies. Sample size calculation was reported in 27% (13/49) of the studies. Only one study assessed the compliance. The causative parasite was not mentioned in 25% (12/49) of the studies and 37% (18/49) of the trials mentioned the endemic nature of the parasite in the area assuming that was the species causing the disease. The timing for outcome assessment was not reported in 4% (2/49) of the trials.

Because resources are limited for clinical research into neglected diseases there is a need to prioritise and carry out properly designed clinical trials. We found many mistakes in the write-up of published manuscripts. Thus, it is essential that submitted journal manuscripts undergo rigorous peer-review.

We found three trials (Alrajhi 2002; Firooz 2005; Firooz 2006) of high quality that fulfilled randomisation, allocation concealment, blinding and ITT adequately. Two of the three RCTs assessed interventions in *L. major* infections (Alrajhi 2002; Firooz 2005) but just one in *L. tropica* infections (Firooz 2006). Thus, better evidence is needed for *L. major* and *L. tropica* infections. We still do not have an ideal treatment profile of one drug that can treat all target species with no or at least no serious adverse effect.

### Potential biases in the review process

The difficulty in determining the actual timing point for cure in clinically significant terms in these studies was due to a lack of any universal measure of successful cure for OWCL. In fact, we found that the majority of the included RCTs did not explore cure rates at least three months after treatment cessation. On the contrary, the primary outcome was assessed at the end of treatment or before three months, in most cases. Indeed, RCTs are needed to explore long-term effects across a group of participants of defined disease severity and duration. For this, it is important to make an *a priori* decision about the post intervention time frame, based on the maximum length of time after the event during which improvement is attributed to the intervention (Goodman 2007).

Some readers might think that our exclusion of non-randomised controlled studies was a bit harsh, especially for studies of antimonials where some reports show high cure rates. Selective reporting of dramatic effects from non-randomised trials without any control group is likely to be misleading although we acknowledge that RCTs (widely accepted as the ideal way of obtaining unbiased estimates of treatment effects) are sometimes not needed for treatments which have dramatic and persistent effects that are highly unlikely to reflect inadequately controlled biases (Glasziou 2007). In other words, the relation between a treatment and its effects is sometimes so dramatic that bias can be ruled out as an explanation without RCTs.

Studies with more positive effects are more likely to be published than those with less conclusive results, or those written in languages other than English (Bigby 2003). To tackle the problem of publication bias we wrote to authors from endemic countries and the WHO asking for information. Besides, we searched databases of ongoing trials and others as well.

### Agreements and disagreements with other studies or reviews

Khatami and colleagues (Khatami 2007) performed a non-Cochrane systematic review on acute Old World cutaneous leishmaniasis. They included 50 studies with a total of 5515 participants. However, we detected quite a few inconsistent results. Firstly, 51 RCTs were cited instead of the 50 claimed in the abstract and the materials and methods, of which 3 (Trau 1987; Dogra 1986; El On 1992) were excluded in our review for several reasons: 1 was a cross-over trial which is an inappropriate design for evaluating potential curative treatments in an infection (El On 1992), and in the other 2 studies, the generation of the randomisation sequence was considered inadequate. Another four trials (Vardy 2001; Mapar 2001; El-Safi 1990; Crawford 2005) were considered non-randomised trials in our review. One RCT (El-On 1985) included in the systematic review performed by Khatami et al dealt with two case reports. Secondly, if clinical trials reported in tables III to VII are included, only 47 studies were mentioned, and 4 of the cited studies were omitted. However we do agree with this review (Khatami 2007) on:

- RCTs were highly variable in quality and methods, providing weak evidence for treatment of OWCL.
- the importance of properly designed RCTs in an attempt to improve their quality and to provide better evidence for the treatment of OWCL.

## AUTHORS' CONCLUSIONS

## Implications for practice

We have produced an updated coverage of randomised controlled trials of treatments for OWCL by summarising the best available evidence using quantitative and qualitative methods. We have endeavoured to provide information to help clinicians choose the most appropriate treatment. We have been careful not to be too prescriptive because the purpose of this systematic review is to present information, rather than offer advice.

We have identified gaps in knowledge. There is no RCT evidence that antimonials, whether intralesional or systemic, are of benefit in treating OWCL. Few treatments for CL have been well evaluated in randomised trials. We found only reasonable RCT evidence of benefit for the use of 200 mg oral itraconazole for 6 weeks in *L. tropica* infections or 200 mg oral fluconazole for 6 weeks, topical 15% paromomycin + 12% MBCL twice daily for 28 days or PDT weekly for 4 weeks in *L. major* infections. In addition, there was reasonable RCT evidence in *L. major* infections that oral pentoxifylline was a good adjuvant therapy to IMMA, IL zinc sulphate weekly up to 6 weeks was ineffective *versus* ILMA, and PDT weekly for 4 weeks was more efficacious than topical 15% paromomycin + 12% MBCL twice daily for 28 days. There was reasonable RCT evidence in *L. tropica* infections that IL SSG was more efficacious than IM administration and thermotherapy was more efficacious than IM SSG. There was reasonable RCT evidence that heat was more efficacious than IMMA administered once a week for four weeks, although the species of *Leishmania* was not reported. There was insufficient RCT evidence to make recommendations on Iocal or systemic administration of MA, oral allopurinol alone or in combination with antimonials, oral ketoconazole, oral dapsone, topical antifungals, IL zinc sulphate or IL hypertonic solution, IL IFN-$\gamma$, physical therapies such as $CO_2$ laser, TCA, and cryotherapy, and finally alternative therapies such as garlic cream or topical herbal extract.

Before starting treatment for localised CL, and especially in the zoonotic form, people with OWCL need to be informed of the possibility of spontaneous healing and the lack of evidence for some treatments. Healthcare practitioners can still play an important role in providing information and wound healing management even if there was no good evidence for any special regimen of healing support. We found no RCTs on the use of wound healing to treat OWCL, but it is frequently used and recommended for the treatment of localised OWCL.

Prevention of blood-borne transmission of other infectious diseases in developing countries includes reduction of injection use, implementation of blood safety practices, and provision of sterile injection equipment.

## Implications for research

Few treatments for OWCL have been well evaluated in randomised trials and we found very few that addressed participant-focused measures of success or measurements of quality of life. Addressing these deficiencies by means of high quality clinical trials has to be a priority and main conclusion from our review. There is a need for more evidence of the effectiveness and safety of different anti-*Leishmania* drugs compared with placebo in self-healing forms of leishmaniasis or with traditional first-line antimonials in complicated form, as the basis to recommend alternative safe, efficacious and affordable treatments.

There have been no trials involving the use of wound healing management or alternative supportive therapies versus drug interventions for OWCL. Special treatment and strategies to be investigated and trials using patient satisfaction outcomes would be invaluable. The development of successful approaches in improving wound healing or reducing scar formation within targeted areas or both, will lead to a reduced risk of developing scars in these sites and are possible future trial priorities.

Resources are particularly limited for research into neglected diseases of the poor and represent major public health problems in developing countries. RCTs require improvement of quality and standardization. Cost and licensing entanglements (freedom to operate) need to be considered before spending money on conducting new trials.

This review suggests that there is some scope for future secondary research by systematically reviewing prevention measures and vaccines in OWCL, and these are already underway within the Cochrane Skin Group.

The ideal schedule of administration is with a single dose of drug or with a short regimen as this improves compliance, or with oral treatments, or as a self administered treatment with no or minimal supervision. The route of administration can be topical but oral is preferred. Last but not least, it should be safe to use on women of childbearing age, on those with co-morbid conditions and in immunocompromised individuals with no drug interactions.

There is much scope for improving the design and reporting of randomised clinical trials in OWCL. To encourage the execution of properly designed clinical trials specifically aimed at the development of effective therapies (both primary and adjuvant), we suggest that future trials should add the following features:

- adequacy of generation of randomisation sequence, allocation concealment, sample size calculation and ITT analysis
- type of causative *Leishmania* species and type of infection
- baseline characteristics should be clearly reported on a table describing age, gender, nationality, history of travel in an endemic area, duration of disease, number and morphology of lesions, sites and severity of lesions, previous treatment taken, and past history of disease scheme for outcome evaluation

- compliance assessment should be described and all information provided
- the time to follow-up should be stated and outcomes should be described accordingly
- detailed definition of inclusion and exclusion criteria: eligible participants should have the presence of lesions parasitologically confirmed as leishmaniasis by direct slit smears and/or skin-punch biopsies of the active, infiltrated edge of a representative lesion, and non-use of anti-*Leishmania* therapy during previous two months.

The current evidence for different types of clinical management of OWCL and for species such as *L. tropica* and *L. aethiopica* is lacking and makes the demand for more research. Prioritisation for clinical research in OWCL is necessary. A more evidence-based strategic approach based on the findings of our systematic review will help to plan and prioritise treatment recommendations and clinical research (Remme 2002a; Remme 2002b).

## ACKNOWLEDGEMENTS

The authors wish to acknowledge: Carmen Chica, William Fabe and Neil Hepburn for their help in writing the protocol; María Ángeles Mora and Rosa Amill for the bibliographical support; Alireza Firooz and Ali Khamesipour for translating and data extraction of the Iranian papers; Mario Tristan and Mayda Villalta for their help in the early development of the review; and Monica Chan for her help to develop this review.

This review has been funded by a grant from the Office of Control of Neglected Tropical Diseases (WHO/CDS/NTD/IDM), Communicable Diseases Cluster, World Health Organization. It has been also supported in part by the International Health Central American Institute Foundation, the Spanish Society of Dermato-Epidemiology and Evidence-based Dermatology (SEDE-DBE), and the Hospital Plató of Barcelona.

The editorial base wishes to thank Richard Reithinger and Philippe Minodier (external expert referees) and Adrian Burton (consumer) for their helpful comments on this review.

## REFERENCES

### References to studies included in this review

**Al-Fouzan 1991** *{published data only}*
Al-Fouzan AS, Al-Saleh QA, Najem NM, Rostom AI. Cutaneous Leishmaniasis in Kuwait. *International Journal of Dermatology* 1991; **30**(7):519–21.

**Alkhawajah 1997** *{published data only}*
Alkhawajah AM, LArbi E, Al-Gindan Y, Abahussein A, Jain S. Treatment of cutaneous leishmaniasis with antimony: intramuscular versus intralesional administration. *Annals of Tropical Medicine and Parasitology* 1997;**91**(8):899–905.

**Alrajhi 2002** *{published data only}*
Alrajhi AA, Ibrahim EA, de Vol EB, Khairat M, Faris RM, Maguire JH. Fluconazole for the treatment of cutaneous leishmaniasis caused by leishmania major. New England Journal of Medicine 2002; Vol. 346, issue 12:891–5.

**Alsaleh 1995** *{published data only}*
Alsaleh Qasem A, Dvorak R, Nanda A. Ketoconazole in the treatment of cutaneous leishmaniasis in Kuwait. *International Journal of Dermatology* 1995;**34**(7):495–7.

**Asilian 1995** *{published data only}*
Asilian A, Jalayer T, Whitworth G, Ghasemi RL, Nilforooshzadeh M, Olliaro P. A randomized, placebo-controlled trial of a two-week regimen of aminosidine (paramomycin) ointment for treatment of cutaneous leishmaniasis in Iran. *The American Journal of Tropical Medicine and Hygiene* 1995;**53**(6):648–51.

**Asilian 2003** *{published data only}*
Asilian A, Jalayer T, Nilforoosshzadeh, Ghassemi RL, Peto R, Wayling S, et al.Treatment of cutaneous leishmaniasis with aminosidine (paromomycin) ointment: double-blind, randomized trial in the Islamic Republic of Iran. *Bulletin of the World Health Organization* 2003;**81**(5):353–9.

**Asilian 2004A** *{published data only}*
Asilian A, Sadeghinia A, Faghihi G, Momeni A. Comparative study of the efficacy of combined cryotherapy and intralesional meglumine antimoniate (glucantime) vs. cryothrapy and intralesional meglumine antimoniate (glucantime) alone for the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* 2004;**43**:281–3.

**Asilian 2004B** *{published data only}*
Asilian A, Sharif A, Faghihi G, Enshaeieh Sh, Shariati F, Siadat AH. Evaluation of $CO_2$ laser efficacy in the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* 2004;**43**:736–8.

**Asilian 2006** *{published data only}*
Asilian A, Davami M. Comparison between the efficacy of photodynamic therapy and topical paromomycin in the treatment of Old World cutaneous leishmaniasis: a placebo-controlled, randomized clinical trial. *Clinics in Dermatology* 2006;**31**:634–7.

**Ben- Salah 1995** *{published data only}*
Ben- Salah AB, Zakraoui H, Zaatour A, Ftaiti A, Zaafouri B, Garraoui A, et al.A randomized, placebo-controlled trial in Tunisia treating cutaneous leishmaniasis with paromomycin ointment. *The American Journal of Tropical Medicine and Hygiene* 1995;**53**(2):162–6.

**Dandashi 2005** *{published data only}*
Dandashi A. Treatment of cutaneous leishmaniasis with fluconazole: a randomized double-blind, placebo-controlled trial. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2005;**19** (Suppl 2):43.

**Dogra 1990** *{published data only}*
Dogra J, Aneja N, Lal Behari B, Mishra SN. Cutaneous Leishmaniasis in India: Clinical Experience with Itraconazole. *International Journal of Dermatology* 1990;**29**(9):661–2.

**Dogra 1991** *{published data only}*
Dogra J. A double-blind study on the efficacy of oral dapsone in cutaneous leishmaniasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1991;**85**:212–3.

**Dogra 1992** *{published data only}*
Dogra J. Cutaneous leishmaniasis in India: evaluation of oral drugs (dapsone versus itraconazole). *European Journal of Dermatology* 1992; **2**:568–9.

**Dogra 1996** *{published data only}*
Dogra J, Saxena VN. Itraconazole and Leishmaniasis: A randomised double-blind trial in cutaneous disease. *International journal for parasitology* 1996;**26**(12):1413–5.

**Esfandiarpour 2002** *{published data only}*
Esfandiarpour I, Alavi A. Evaluating the efficacy of allopurinol and meglumine antimoniate (glucantime) in the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* 2002;**41**:521–4.

**Faghihi 2003** *{published data only}*
Faghihi G, Tavakoli-kia R. Topical paromomycin vs intralesional meglumine antimoniate in cutaneous leishmaniasis. *Clinical and Experimental Dermatology* 2003;**28**(1):13–6.

**Firooz 2005** *{published data only}*
Firooz A, Khatami A, Khamesipour A, Nassiri-Kashani M, Behnia F, Nilforoushzadeh M, et al.Intralesional injection of 2% zinc sulphate solution in the treatment of acute Old World cutaneous leishmaniasis: a randomized, double-blind, controlled clinical trial. *Journal of Drugs in dermatology: JDD* 2005;**4**(1):73–9.

**Firooz 2006** *{published data only}*
Firooz A, Khamesipour A, Ghoorchi MH, Nassiri-Kashani M, Ebrahim Eskandari S, Khatami A, et al.Imiquimod in combination with meglumine antimoniate for cutaneous leishmaniasis: a randomized assessor-blind controlled trial. *Archives of Dermatology* 2006; **142**:1575–9.

**Gholami 2000** *{published data only}*
* Gholami A, Khamesipour A, Momeni A, Ghazanfari T, Nilforoushzadeh MA, Darajeh Z, et al.Treatment of cutaneous leishmaniasis with 5% garlic cream: a randomized, double-blind study. *Iranian Journal of Dermatology* 2000;**3**(3):2–6.

**Harms 1991** *{published data only}*
Harms G, Chehade AK, Douba M, Roepke M, Mouakeh A, Rosenkaimer F, et al.A randomized trial comparing a pentavalent antimonial drug and recombinant interfferon in the local treatment of cutaneous leishmaniasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1991;**85**:214–6.

**Iraji 2004** *{published data only}*
Iraji F, Vali A, Asilian A, Shahtalebi M, Momeni AZ. Comparison of intralesionally injected Zinc sulphate with Meglumine Antimoniate in the treatment of acute cutaneous leishmaniasis. *Dermatology* 2004; **209**:46–9.

**Iraji 2005** *{published data only}*
Iraji F, Sadeghinia A. Efficacy of paromomycin ointment in the treatment of cutaneous leishmaniasis: results of a double-blind, randomized trial in Isfahan, Iran. *Annals of tropical medicine and parasitology* 2005;**99**(1):3–9.

**Jaffar 2006** *{published data only}*
Jaffar H. Rifampicin in cutaneous leishmaniasis- a therapeutic trial in Saudi Arabia. *Journal of Pakistan Association of Dermatologists* 2006; **16**:4–9.

**Kochar 2000** *{published data only}*
Kochar DK, Aseri S, Sharma BV, Bumb RA, Mehta RD, Purohit SK. The role of rifampicin in the management of cutaneous leishmaniasis. *Oxford University Press* 2000;**93(11)**:733–7.

**Kochar 2006** *{published data only}*
Kochar DK, Saini G, Kochar SK, Sirohi P, Bumb RA, Mehta RD, et al.A double blind, randomised placebo controlled trial of rifampicin with omeprazole in the treatment of human cutaneous leishmaniasis. *Journal of vector borne diseases* 2006;**43**:161–7.

**Larbi 1995** *{published data only}*
Larbi EB, Al-Khawajah A, Al-gindan Y, Jain S, Abahusain A, Al-Zayer A. A randomized, double-blind, clinical trial of topical clotrimazole versus mizonazole for treatment of cutaneous leishmaniasis in the eastern province of Saudi Arabia. *The American Journal of Tropical Medicine and Hygiene* 1995;**52**(2):166–8.

**Lynen 1992** *{published data only}*
Lynen L, Van Damme W. Local application of Diminazene aceturate: an effective treatment for cutaneous Leishmaniasis?. *Annales de la Société belge de médecine tropicale* 1992;**72**:13–9.

**Mashood 2001** *{published data only}*
Mashood AA, Hussain K. Efficacy of allopurinol compared with pentostam in the treatment of old worls cutaneous leishmaniasis. *Journal of the College of Physicians and Surgeons--Pakistan : JCPSP* 2001;**11** (6):367–70.

**Mohebali 2007** *{published data only}*
Mohebali M, Fotouhi A, Hooshmand B, Zarei Z, Akhoundi B, Rahnema A, et al.Comparison of miltefosine and meglumine antimoniate for the treatment of zoonotic cutaneous leishmaniasis (ZCL) by a randomized clinical trial in Iran. *Acta tropica* 2007;**103**:33–40.

**Momeni 1996** *{published data only}*
Momeni AZ, Jalayer T, Emamjomeh M, Bashardost N, Ghassemi RL, Meghdadi M, et al.Treatment of cutaneous leishmaniasis with itraconazole. *Archives of Dermatology* 1996;**132**:784–6.

**Momeni 2002** *{published data only}*
Momeni AZ, Reiszadae MR, Aminjavaheri M. Treatment of cutaneous leishmaniasis with a combination of allopurinol and low-dose meglumine antimoniate. *International Journal of Dermatology* 2002; **41**:441–3.

**Momeni 2003** *{published data only}*
* Momeni AZ, Aminjavaheri M, Omidghaemi MR. Treatment of cutaneous leishmaniasis with ketoconazole cream. *The Journal of Dermatological Treatment* 2003;**14**(1):26–9.

**Mujtaba 1999** *{published data only}*
* Mujtaba G, Khalid M. Weekly vs fortnightly intralesional meglumine antimoniate in cutaneous leishmaniasis. *International Journal of Dermatology* 1999;**38**(8):607–9.

**Nassiri-Kashani 2005** *{published data only}*
Nassiri-Kashani M, Firooz A, Khamesipour A, Mojtahed F, Nilforoushzadeh M, Hejazi H, et al.A randomized, double-blind,

placebo-controlled clinical trial of itraconazole in the treatment of cutaneous leishmaniasis. *Journal of the European Academy of Dermatology and Venereology: JEADV* 2005;**19**:80–3.

**Nilforoushzadeh 2004** *{published data only}*
Nilforoushzadeh MA. Efficacy of combined triple therapy (paromomycin ointment, cryotherapy and intralesional Glucantime) in comparison with intralesional Glucantime for treatment of acute cutaneous leishmaniasis. *Iranian Journal of Dermatology* 2004;**3**(7): 136–9.

**Nilforoushzadeh 2006** *{published data only}*
Nilforoushzadeh MA, Jaffary F, Reiszadeh MR. Comparative effect of topical trichloroacetic acid and intralesional meglumine antimoniate in the treatment of acute cutaneous leishmaniasis. *International Journal of Pharmacology* 2006;**2**(6):633–6.
Nilforoushzadeh MA, Reiszadeh MR, Jafari F. Topical trichloroacetic acid compared with intralesional glucantime injection in the treatment of acute wet cutaneous leishmaniasis: An open clinical trial. *Iranian Journal of Dermatology* 2003;**2**(6):34–9.

**Nilforoushzadeh 2007** *{published data only}*
Nilforoushzadeh MA, Jaffary F, Moradi S, Derakhshan R, Haftbaradaran E. Effect of topical honey application along with intralesional injection of glucantime in the treatment of cutanneous leishmaniasis. *BMC complementary and alternative medicine* 2007;**7**:13.

**Reithinger 2005** *{published data only}*
Reithinger R, Mohsen M, Wahid M, Bismullah M, Quinnell RJ, Davies CR, et al.Efficacy of thermotherapy to treat cutaneous leishmaniasis caused by Leishmania tropica in Kabul, Afghanistan: a randomized, controlled trial. *CID* 2005;**40**:1148–54.

**Sadeghian 2006** *{published data only}*
Sadeghian G, Nilforoushzadeh MA. Effect of combination therapy with systemic glucantime and pentoxifylline in the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* 2006;**45**: 819–21.

**Sadeghian 2006B** *{published data only}*
Sadeghian G, Nilfroushzadeh MA, Siadat AH. A comparison between intralesional hypertonic sodium chloride solution and meglumine antimoniate in the treatment of cutaneous leishmaniasis. *Egyptian Dermatology Online Journal* 2;**1**:8.

**Sadeghian 2007** *{published data only}*
Sadeghian G, Nilfroushzadeh MA, Iraji F. Efficacy of local heat therapy by radiofrequency in the treatment of cutaneous leishmaniasis, compared with intralesional injection of meglumine antimoniate. *Clinical and Experimental Dermatology* 2007;**32**(4):371–4.

**Salmanpour 2001** *{published data only}*
Salmanpour R, Handjani F, Noupisheh MK. Comparative study of the efficacy of oral ketoconazole with intra-lesional meglumine antimoniate (glucantime) for the treatment of cutaneous leishmaniasis. *The Journal of Dermatological Treatment* 2001;**12**:159–62.

**Salmanpour 2006** *{published data only}*
Salmanpour R, Razmavar MR, Abtahi N. Comparison of intralesional meglumine antimoniate, cryotherapy and their combination in the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* 2006;**45**(9):1115–6.

**Sharquie 1997** *{published data only}*
Sharquie KE, Najim RA, Farjou IB. A compararive controlled trial of intralesionally- administered zinc sulphate, hypertonic sodium chloride and pentavalent antimony compound against cutaneous leishmaniasis. *Clinical and Experimental Dermatology* 1997;**22**(4):169–73.

**Sharquie 2001** *{published data only}*
Sharquie KE, Najim RA, Farjou IB, Al-timimit DJ. Oral Zinc sulphate in the treatment of acute cutaneous leishmaniasis. *Clinics in dermatology* 2001;**26**:21–6.

**Shazad 2005** *{published data only}*
Shazad B, Abbaszadeh B, Khamesipour A. Comparison of topical paromomycin sulfate (twice/day) with intralesional meglumine antimoniate for the treatment of cutaneous leishmaniasis caused by L.major. *European Journal of Dermatology* 2005;**15**(2):85–7.

**Zerehsaz 1999** *{published data only}*
Zerehsaz F, Salmanpour R, Farhad H, Ardehali S, Panjehshahin MR, Tabei SZ, et al.A double-blind randomized clinical trial of a topical herbal extract (Z-HE) vs. systemic meglumine antimoniate for the treatment of cutaneous leishmaniasis in Iran. *International Journal of Dermatology* 1999;**38**(8):610–2.

**Özgöztasi 1997** *{published data only}*
Özgöztasi O, Baydar I. A randomized clinical trial of topical paromomycin versus oral ketoconazole for treating cutaneous leishmaniasis in Turkey. *International Journal of Dermatology* 1997;**36**(1):61–3.

## References to studies excluded from this review

**Dogra 1986** *{published data only}*
Dogra J, Behari Lal B, Nath Misra S. Dapsone in the treatment of Cutaneous Leishmaniasis. *International Journal of Dermatology* 1986;**25**(6):398–400.

**Dogra 1994** *{published data only}*
Dogra J, Aneja N. Leishmaniasis and itraconazole: a controlled clinical trial on cutaneous subtypes. *International journal of antimicrobial agents* 1994;**4**:309–11.

**El On 1992** *{published data only}*
El-On J, Halevy S, Grunwald MH, Weinrauch L. Topical treatment of Old World cutaneous leishmaniasis caused by leishmania major: a double blind control study. *Journal of the American Academy of Dermatology* 1992;**27**:227–31.

**Frankenburg 1993** *{published data only}*
Frankenburg S, Gross A, Jonas F, Klaus S. Effect of topical paromomycin on cell-mediated immunity during cutaneous leishmaniasis. *International Journal of Dermatology* 1993;**32**(1):68–70.

**Moosavi 2005** *{published data only}*
Moosavi Z, Nakhli A, Rassaii S. Comparing the efficiency of topical paromomycin with intralesional meglumine antimoniate for cutaneous leishmaniasis. *International Journal of Dermatology* 2005;**44** (12):1064–5.

**Singh 1995** *{published data only}*
Singh S, Singh R, Sundar S. Failure of Ketaconazole in oriental sore in India. *Journal of Chemotherapy* 1995;**7**(4):202–3.

**Trau 1987** *{published data only}*
Trau H, Schewach-Millet M, Shoham J, Doerner T, Shor R, Passwell JH. Topical application of Human fibroblast interferon (IFN) in

cutaneous Leishmaniasis. *Israel Journal of Medical Sciences* 1987;**23**: 1125–7.

## References to studies awaiting assessment

**Layegh 2007** *{published data only}*

Layegh P, Yazdanpanah M J, Vosugh EM, Pezeshkpoor F, Shakeri M T, Moghiman T. Efficacy of azithromycin versus systemic meglumine antimoniate (Glucantime) in the treatment of cutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 2007;**77**(1): 99–101.

## References to ongoing studies

**ISRCTN32701387** *{published data only}*

Nilforoushzadeh M. A comparative study of the efficacy of combination therapy with oral omeprazole and low dose of systemic meglumine antimoniate versus the standard dose of systemic meglumine antimoniate in the treatment of cutaneous leishmaniasis. ClinicalTrials.gov.

**NCT00480883** *{published data only}*

Ejaz A. Treatment of Cutaneous Leishmaniasis With Meglumine Antimoniate 20 Mg/Kg/Day Versus Meglumine Antimoniate 10 Mg/Kg/Day And Tablet Allopurinol 20 Mg/Kg/Day. ClinicalTrials.gov.

**NCT00606580** *{unpublished data only}*

A Pivotal, Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate WR 279,396 and Paromomycin Alone to Treat Cutaneous Leishmaniasis (in Tunisia). Ongoing study Date of first enrolment: January 2008.

## Additional references

**Alrajhi 2003**

Alrajhi AA. Cutaneous leishmaniasis of the Old World. *Skin therapy letter* 2003;**8**(2):1–4.

**Alvar 2006**

Alvar J, Yactayo S, Bern C. Leishmaniasis and poverty. *Trends in Parasitology* 2006;**22**(12):552–7.

**Alvar 2008**

Alvar J, Aparicio P, Aseffa A, den Boer M, Cañavate C, Dedet JP, et al.The Relationship between Leishmaniasis and AIDS: The Second 10 Years.. *Clinical Microbiology Review* 2008;**2**:334–59.

**Aram 1987**

Aram H, Leibovici V. Ultrasound-induced hyperthermia in the treatment of cutaneous leishmaniasis. *Cutis* 1987;**40**:350–3.

**Arevalo 2007**

Arevalo I, Tulliano G, Quispe A, Spaeth G, Mathlashewski, LLanoscuantas A, et al.Role of imiquimod and parenteral meglumine antimoniate in the intitial treatment of cutaneous lesihmaniasis. *CID* 2007;**44**:1549–54.

**Babajev 1991**

Babajev KB, Babajev OG, Korepanov VI. Treatment of cutaneous leishmaniasis using a carbon dioxide laser. *Bulletin of the World Health Organization* 1991;**69**:103–6.

**Badaro 1990**

Badaro R, Falcoff E, Badaro FS, Carvalho EM, Pedral-Sampaio D, Barral A, et al.Treatment of visceral leishmaniasis with pentavalent antimony and interferon gamma. *New England Journal of Medicine* 1990;**322**(1):16–21.

**Baryza 1995**

Baryza MJ, Baryza GA. The Vancouver Scar Scale: an administration tool and its interrater reliability. *Journal of Burn Care Rehabilitation* 1995;**16**(5):535–8.

**Bassiouny 1982**

Bassiouny A, El Meshad M, Talaat M, Kutty K, Metawaa B. Cryosurgery in cutaneous leishmaniasis. *British Journal of Dermatology* 1982;**107**(4):467–74.

**Berman 1981**

Berman JD, Neva FA. Effect of temperature on multiplication of Leishmania amastigotes within monocyte-derived macrophages in vitro. *The American journal of tropical medicine and hygiene* 1981;**30**: 318–21.

**Berman 2005**

Berman J. Miltefosine to treatment leishmaniasis: drug evaluation. *Expert Opinion on Investigational drugs* 2005;**6**(8):1381–8.

**Bigby 2003**

Bigby M, Williams H. Appraising Systematic Reviews and Meta-analyses. *Archives of Dermatology* 2003;**139**:795–798.

**Bogenrieder 2003**

Bogenrieder T, Lehn, N, Landthaler M, Stolz, W. Treatment of Old World cutaneous leishmaniasis with intralesionally injected meglumine antimoniate using a Dermojet device. *Dermatology* 2003;**206** (3):269–72.

**Borelli 1987**

Borelli D. A clinical trial of itraconazole in the treatment of deep mycoses and leishmaniasis. *Reviews of infectious diseases* 1987;**9**(1): S57–63.

**Bryceson 1994**

Bryceson ADM, Murphy A. Treatment of cutaneous leishmaniasis of the Old World with aminosidine ointment:results of an open study in patients in London. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994;**88**:226–8.

**Bygbjerg 1980**

Bygbjerg IC, Knudsen L, Kieffer M. Failure of rifampicin therapy to cure cutaneous leishmaniasis. *Archives of Dermatology* 1980;**116**: 988.

**Cauwenberg 1986**

Cauwenberg G, Doncker PD. Itraconazole (R 51 211): a clinical review of its anti mycotic activity in dermatology, gynecology, and internal medicine. *Drug development research* 1986;**8**:317–23.

**Chulay 1983**

Chulay JD, Anzeze EM, Koech DK, Bryceson AD. High-dose sodium stibogluconate treatment of cutaneous leishmaniasis in Kenya. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1983;**77**(5):717–21.

**Chunge 1985**

Chunge CN, Gachihi G, Muigai R, Wasunna K, Rashid JR, Chulay JD, et al.Visceral leishmaniasis unresponsive to antimonial drugs. III. Successful treatment using a combination of sodium stibogluconate plus allopurinol. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1985;**79**:715–8.

**Crawford 2005**
Crawford R, Holmes D, Meymandi S. Comparative study of the efficacy of combined imiquimod 5% cream and intralesional meglumine antimoniate versus imiquimod 5% cream and intralesional meglumine antimoniate alone for the treatment of cutaneous leishmaniasis. *Journal of the American Academy of Dermatology* 2005;**52**: S118.

**Croft 2006**
Croft SL, Seifert K, Yardley V. Current scenario of drug development for Leishmaniasis. *The Indian journal of medical research* 2006;**123** (3):399–410.

**Davis 2003**
Davies CR, Kaye P, Croft SL, Sundar S. Leishmaniasis: new approaches to disease control. *BMJ* 2003;**326**(7385):377–82.

**Desjeux 1996**
Desjeux P. Leishmaniasis. Public health aspects and control. *Clinical Dermatology* 1996;**14**:417–23.

**El-On 1985**
el-On J, Weinrauch L, Livshin R, Even-Paz Z, Jacobs GP. Topical treatment of recurrent cutaneous leishmaniasis with ointment containing paromomycin and methylbenzethonium chloride. *BMJ* 1985;**291**(6497):704–5.

**El-Safi 1990**
El-Safi SH, Murphy AG, Bryceson ADM, Neal RA. A double-blind clinical trial of the treatment of cutaneous leishmaniasis with paromomycin ointment. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1990;**84**:690–1.

**Enk 2003**
Enk CD, Fritsch C, Jonas F, Nasereddin A, Ingber A, Jaffe CL, et al.Treatment of cutaneous leishmaniasis with photodynamic therapy. *Archives of Dermatology* 2003;**139**(4):432–4.

**Faber 2003**
Faber WR, Oskam L, Gool T van, Kroon NCM, Knegt-Junk KJ, Hofwegen H, et al.Value of diagnostic techniques for cutaneous leishmaniasis. *Journal of the American Academy of Dermatology* 2003;**49**: 70–4.

**Garnier 2006**
Garnier T, Brown, MB, Lawrence, M J, Croft, L. In-vitro and in-vivo studies on a topical formulation of sitamaquine dihydrochloride for cutaneous leishmaniasis. *The Journal of pharmacy and pharmacology* 58;**8**:1043–54.

**Glasziou 2007**
Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. *British Medical Journal* 2007;**334**(7589):349–51.

**Gonzalez 2004**
González U, Ospina EG, Rengifo-Pardo M, Macaya A, Tweed J. Interventions for American cutaneous and mucocutaneous leishmaniasis. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD004834]

**Goodman 2007**
Goodman AC. Beware the "Texas sharp shooter" in rate ratios of progression. *British Medical Journal* 2007;**334**(7591):440.

**Hepburn 2001**
Hepburn NC. Management of cutaneous leishmaniasis. *Current Opinion in Infectious Diseases* 2001;**14**:151–4.

**Herwaldt 1999**
Herwaldt B.L. Leishmaniasis. *Lancet* 1999;**354**:1191–9.

**Iqbal 2006**
Iqbal J, Bukhari I, Jamshid M, Bashir S, Masoom Yasinzai M, et al.Hexadecyl-phosphorylcholine ointment for treatment of cutaneous leishmaniasis: an animal trial. *Eastern Mediterranean health journal* 2006;**12**(5):685–9.

**Jha 1983**
Jha TK. Evaluation of allopurinol in the treatment of kala-azar occurring in North Bihar, India. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1983;**77**:204–7.

**Jiang 2002**
Jiang S, Meadows J, Anderson SA, Mukkada AJ. Antileishmanial activity of the antiulcer agent omeprazole. *Antimicrobial agents and chemotherapy* 2002;**46**(8):2569–74.

**Junaid 1986**
Junaid AJN. Treatment of cutaneous leishmaniasis with infrared heat. *International Journal of Dermatology* 1986;**25**:470–2.

**Juni 2001**
Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled trials. *BMJ* 2001;**323**:42–6.

**Kager 1981**
Kager PA, Rees PH, Wellde BT, Hockmeyer WT, Lyerly WH. Allopurinol in the treatment of visceral leishmaniasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1981;**75**:556–9.

**Karamian 2007**
Karamian M, Motazedian MH, Mehrabani D, Gholami K. Leishmania major infection in a patient with visceral leishmaniasis: treatment with Amphotericin B. *Parasitology research* 2007;**101**(5):1431–4.

**Khalid 2005**
Khalid FA, Abdalla NM, O.Mohomed HE, Toum AM, A. Magzoub MM, Ali MS. In vitro Assessment of Anti - Cutaneous Leishmaniasis Activity of Some Sudanese Plants. *Türkiye Parazitoloji Dergisi* 2005; **29**(1):3–6.

**Khan 2005**
Khan SJ, Muneeb S. Cutaneous leishmaniasis in Pakistan. *Dermatology Online Journal* 2005;**11**(1):4.

**Khatami 2007**
Khatami A, Firooz A, Gorouhi F, Dowlati Y. Treatment of acute Old World cutaneous leishmaniasis: a systematic review of the randomized controlled trials. *Journal of the American Academy of Dermatology* 2007;**57**(2):335.e1–29.

**Laguna 1999**
Laguna F, López-Vélez R, Pulido F, Salas A, Torre-Cisneros J, Torres E, et al.Treatment of visceral leishmaniasis in HIV-infected patients: a randomized trial comparing meglumine antimoniate with amphotericin B. Spanish HIV-Leishmania Study Group. *AIDS* 1999;**13** (9):1063–9.

**Leibovici 1986**
Leibovici V, Aram H. Cryotherapy in acute cutaneous leishmaniasis. *International Journal of Dermatology* 1986;**25**(7):473–5.

**Lessa 2001**

Lessa HA, Machado P, Lima F, Cruz AA, Bacellar O, Guerreiro J, et al.Successful treatment of refractory mucosal leishmaniasis with pentoxifylline plus antimony. *The American journal of tropical medicine and hygiene* 2001;**65**(2):87–9.

**Levine 1992**

Levine N. Cutaneous leishmaniasis treated with controlled localized heating. *Archives of Dermatology* 1992;**128**(6):759–61.

**Mapar 2001**

Mapar MA, Kavoosi H, Dabbagh MA. Assessment of the effect of topical opium in treatment of cutaneous leishmaniasis. *Iranian Journal of Dermatology* 2001;**4**(4):23–8.

**Markle 2004**

Markle WH, Makhoul K. Cutaneous leishmaniasis: recognition and treatment. *American Family Physician* 2004;**69**(6):1455–60.

**Meawad 1997**

Meawad OB. Selective heat therapy in cutaneous leishmaniasis: a preliminary experience using the 585 nm pulsed dye laser. *Journal of the European Academy of Dermatology and Venereology : JEADV* 1997; **8**:241–4.

**Minodier 2007**

Minodier P, Parola P. Cutaneous leishmaniasis treatment. *Travel medicine and infectious disease* 2007;**5**(3):150–8.

**Modabber 2007**

Modabber F, Buffet PA, Torreele E, Milon G, Croft SL. Consultative meeting to develop a strategy for treatment of cutaneous leishmaniasis. Institute Pasteur, Paris. 13-15 June, 2006. *Kinetoplastid biology and disease* 2007;**6**:3.

**Moore 2001**

Moore OA, Smith LA, Campbell F, Seers K, McQuay KJ, Moore RA. Systematic review of the use of honey as a wound dressing. *BMC complementary and alternative medicine* 2001;**1**:2.

**Moskowitz 1999**

Moskowitz PF, Kurban AK. Treatment of cutaneous leishmaniasis: Retrospective and advances for the 21st century. *Clinical Dermatology* 1999;**17**:305–15.

**Musa 2005**

Musa AM, Khalil EA, Mahgoub FA, Hamad S, Elkadaru AM, El Hassan AM. Efficacy of liposomal amphotericin B (AmBisome) in the treatment of persistent post-kala-azar dermal leishmaniasis (PKDL). *Annals of tropical medicine and parasitology* 2005;**99**(6):563–9.

**Najim 1998**

Najim RA, Sharquie KE, Farjou IB. Zinc sulphate in the treatment of cutaneous leishmaniasis: an in vitro and animal study. *Memórias do Instituto Oswaldo Cruz* 1998;**93**:831–7.

**Navin 1990**

Navin TR, Arana BA, Arana FE, de Mérida AM, Castillo AL, Pozuelos JL. Placebo-controlled clinical trial of meglumine antimoniate (glucantime) versus localized controlled heat in the treatment of cutaneous leishmaniasis in Guatemala. *The American journal of tropical medicine and hygiene* 1990;**42**(1):43-50 (89-153).

**Neva 1984**

Neva FA, Petersen EA, Corsey R, Bogaert H, Martinez D. Observations on local heat treatment for cutaneous leishmaniasis. *The American journal of tropical medicine and hygiene* 1984;**33**:800–4.

**Passwell 1986**

Passwell JH, Shor R, Shoham J. The enhancing effect of interferon-beta and -gamma on the killing of Leishmania tropica major in human mononuclear phagocytes in vitro. *Journal of immunology* 1986; **136**(8):3062–6.

**Pieper 2003**

Pieper B, Caliri Mh. Nontraditional wound care: A review of the evidence for the use of sugar, papaya/papain, and fatty acids. *Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society / WOCN* 2003;**30**(4): 175–83.

**Ponte-Sucre 2003**

Ponte-Sucre A. Physiological consequences of drug resistance in Leishmania and their relevance for chemotherapy. *Kinetoplastid biology and disease* 2003;**2**(1):14.

**R-Cuartero 1990**

Rodriguez-Cuartero A, Pérez-Blanco FJ, López-Fernández A. Cotrimoxazole for visceral leishmaniasis. *Infection* 1990;**18**(1):40.

**Rathi 2005**

Rathi SK, Pandhi RK, Chopra P, Khanna N. Post-kala-azar dermal leishmaniasis: a histopathological study. *Journal of dermatology, venereology and leprology* 2005;**71**(4):250–53.

**Reithinger 2005B**

Reithinger R, Aadil K, Kolaczinski J, Mohsen M, Hami S. Social impact of leishmaniasis, Afghanistan. *Emerging infectious diseases* 2005;**11**(4):634–6.

**Reithinger 2007**

Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. *The Lancet infectious diseases* 2007;**7**(9):581–96.

**Remme 2002a**

Remme JH, Blas E, Chitsulo L, Desjeux PM, Engers HD, Kanyok TP, et al.Strategic emphases for tropical diseases research: a TDR perspective. *Trends in Parasitology* 2002;**18**(10):421–26.

**Remme 2002b**

Remme JHF, Blas E, Chitsulo L, Desjeux PM, Engers HD, Kanyok TP, et al.Strategic emphases for tropical diseases research: a TDR prespective. *Trends in Microbiology* 2002;**10**(10):435–40.

**Rodriguez 1990**

Rodriguez ME, Inguanzo P, Ramos A, Perez J. Treatment of cutaneous leishmaniasis with $CO_2$ laser radiation. *Revista cubana de medicina tropical* 1990;**42**:197–202.

**Sacks 1983**

Sacks DL, Barral A, Neva F. Thermosensitivity patterns of Old vs. New World cutaneous strains of Leishmania growing within mouse peritoneal macrophages in vitro. *The American journal of tropical medicine and hygiene* 1983;**32**:300–4.

**Sampaio 1960**

Sampaio SA, Godoy JT, Paiva L, Dillon NL, da Lacaz CS. The treatment of American (mucocutaneous) leishmaniasis with amphotericin B. *Archives of Dermatology* 1960;**82**:627–35.

**Sampaio 1997**

Sampaio RN, Marsden PD. Treatment of the mucosal form of leishmaniasis without response to glucantime, with liposomal ampho-

tericin B. *Revista da Sociedade Brasileira de Medicina Tropical* 1997; **30**(2):125–8.

**Savioli 2006**

Savioli L, Engels D, Daumerie D, Jannin J, Alvar J, Asiedu K, et al.Response from Savioli and colleagues from the Department of Neglected Tropical Diseases, World Health Organization. *PLoS medicine* 2006;**3**(6):e283.

**Schalling 2002**

Schalling DFH, Oskam L. Molecular biological applications in the diagnosis and control of leishmaniasis and parasite identification. *Tropical Medicine and International Health* 2002;**7**:641–51.

**Sharquie 1995**

Sharquie KE. A new intralesional therapy for cutaneousd leishmaniasis with hypertonic sodium chloride solution. *Journal of Dermatology (Japan)* 1995;**22**:732–7.

**Sharquie 1996**

Sharquie KE, Al- Azzawi KE. Intralesional therapy for cutaneous leishmaniasis with 2% zinc sulfate solution. *Journal of Pan-Arab League of Dermatologists* 1996;**7**:41–6.

**Sharquie 1998**

Sharquie KE, Al-Hamamy H, El- Yassin D. Treatment of cutaneous leishmaniasis by direct current electrotherapy: the Baghdadin device. *Journal of Dermatology* 1998;**25**:234–7.

**Sherwood 1994**

Sherwood JA, Gachihi GS, Muigai RK, Skillman DR, Mugo M, Rashid JR, et al.Phase 2 efficacy trial of an oral 8-aminoquinoline (WR6026) for treatment of visceral leishmaniasis. *CID* 1994;**19**(6): 1034–9.

**Sindermann 2006**

Sindermann H, Engel J. Development of miltefosine as an oral treatment for leishmaniasis. *Transactions of the royal Society of Tropical Medicine and Hygiene* 2006;**100**:S17–20.

**Soto 2004**

Soto J, Arana BA, Toledo J, Rizzo N, Vega JC, Diaz A, et al.Miltefosine for new world cutaneous leishmaniasis. *CID* 2004;**38**: 1266–72.

**Stojkovic 2007**

Stojkovic M, Junghanss T, Krause E, Davidson RN. First case of typical Old World cutaneous leishmaniasis treated with miltefosine. *International Journal of Dermatology* 2007;**6**(4):385–7.

**Sundar 2006**

Sundar S, Chatterjee M. Visceral leishmaniasis - current therapeutic modalities. *The Indian journal of medical research The Indian journal of medical research* 2006;**123**(3):345–52.

**Sundar 2007A**

Sundar S, Chakravarty J, Rai VK, Agrawal N, Singh SP, Chauhan V, et al.Amphotericin B treatment for Indian visceral leishmaniasis: response to 15 daily versus alternate-day infusions. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2007;**45**(5):556–61.

**Sundar 2007B**

Sundar S, Jha TK, Thakur CP, Sinha PK, Bhattacharya SK. Injectable paromomycin for Visceral leishmaniasis in India. *New England Journal of Medicine* 2007;**356**(25):2571–81.

**Teklemariam 1994**

Teklemariam S, Hiwot AG, Frommel D, Miko TL, Ganlov G, Bryceson A. Aminosidine and its combination with sodium stibogluconate in the treatment of diffuse cutaneous leishmaniasis caused by Leishmania aethiopica. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994;**88**(3):334–9.

**Thakur 1996**

Thakur CP, Pandey AK, Sinha GP, Roy S, Behbehani K, Olliaro P. Comparison of three treatment regimens with liposomal amphotericin B (AmBisome) for visceral leishmaniasis in India: a randomized dose-finding study. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1996;**90**(3):319–22.

**Urcuyo 1982**

Urcuyo FG, Zaias N. Oral ketoconazole in the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* 1982;**21**:414–6.

**V-Castrejon 1997**

Velasco-Castrejon O, Walton BC, Rivas-Sanchez B, Garcia MF, Lazaro GJ, Hobart O, et al.Treatment of cutaneous leishmaniasis with localized current field (radio frequency) in Tabasco, Mexico. *The American journal of tropical medicine and hygiene* 1997;**57**(3): 309–12.

**Vaneau 2007**

Vaneau M, Chaby G, Guillot B, Martel P, Senet P, Téot L, et al.Consensus panel recommendations for chronic and acute wound dressings. *Archives of Dermatology* 2007;**143**(10):1291–4.

**Vardy 2001**

Vardy D, Barenholz Y, Naftoliev N, Klaus S, Gilead L, Frankenburg S. Efficacious topical treatment for human cutaneous leishmaniasis with ethanolic lipid amphotericin B. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2001;**95**(2):184–6.

**Weigel 2001**

Weigel MM, Armijos RX. The traditional and conventional medical treatment of cutaneous leishmaniasis in rural Ecuador. *Revista panamericana de salud pública = Pan American journal of public health* 2001;**10**(6):395–404.

**Weinrauch 1983a**

Weinrauch L, Livshin R, El-On J. Cutaneous leishmaniasis treatment with ketoconazole. *Cutis* 1983;**32**(3):288–90.

**Weinrauch 1983b**

Weinrauch L, Livshin R, Even-Paz Z, El-On J. Efficacy of ketoconazole in cutaneous leishmaniasis. *Archives of Dermatology* 1983;**275** (5):353–4.

**WHO 2001**

World Health Organization. WHO Report on global surveillance of epidemic-prone infectious diseases.. http://www.who.int/emc-documents/surveillance/docs/whocdscsrisr2001.html/Leishmaniasis/Leishmaniasis.htm 2001, issue date last accessed: 2/4/2004.

**WHO 2002**

World Health Organization (WHO). Leishmaniasis. World Health Report 2002. http://www.who.int/whr/2002/annex/en/ 2002, issue date last accessed: 2/4/2004.

**WHO 2007**

World Heald Organisation. Control of leishmaniasis. Report by the Secretariat. http://ftp.who.int/gb/ebwha/pdf_files/WHA60/A60_10-en.pdf 22 March 2007.

**WHO 2008, in press**
World Health Organization (WHO). Report of the Fifth Consultatve Meeting on HIV-Leishmania co-infection. Addis Ababa, 20 to 22 March 2007. WHO/CDS/NTD/IDM/2007 2008 (in press).
* *Indicates the major publication for the study*

# CHARACTERISTICS OF STUDIES

## Characteristics of included studies *[ordered by study ID]*

**Al-Fouzan 1991**

| | |
|---|---|
| Methods | FU:12 weeks post-treatment<br>D: Randomised clinical trial |
| Participants | Kuwait<br>n = 24<br>M/F: 13/11, with an age range from 12 to 52 years old. Lesions: single or multiple lesions, active being nodule, nodule-ulcerative, or ulcerative. The site of lesions including both groups was 75% on upper limbs; 46% on lower limbs; 25% on the face and 4% on the trunk. The duration of the lesion varied between 1 and 14 months.<br>Baseline comparability: no mention of comparability only stated after randomisation, age and sex matched in each group.<br>Incl: Proved positive for leishmania parasites (amastigotes) on microscopic examination. Women of childbearing age were instructed to use potent and adequate contraceptive measures before the initiation of treatment.<br>*Leishmania* species: *L. tropica* or *L. major* in the area. |
| Interventions | T1: Oral itraconazole 200 mg TD for 6 to 8 weeks<br>There was a 12 year old boy who was given a dose of 100 mg once daily (3 mg/kg per day)<br>n = 15.<br>T2: Placebo capsules TD during meals for 6 to 8 weeks<br>n = 9 |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' two months after treatment<br>*Secondary outcomes*<br>Duration of remission and percentage of people with treated lesions that recur within six months, one, two and three years (for a period up to three months after suspension of the drug)<br>Adverse effects |
| Notes | Sample size: Small/ NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|

**Al-Fouzan 1991** (*Continued*)

| | | |
|---|---|---|
| Blinding?<br>All outcomes | Unclear | no mention about blinding, it stated that the capsules were identical in appearance |
| Intention-to-treat/Drop-outs? | Yes | ND |

**Alkhawajah 1997**

| | |
|---|---|
| Methods | FU: one month post-treatment<br>D: Randomised clinical trial |
| Participants | Saudi Arabia<br>n = 80 (only 67 completed the study)<br>Px with CL in the Eastern province of Saudi Arabia, in Al-Ahssa. M/F: 48/19, with an age range of 13 to 42 years old. Lesion type in the IMMA group were: Nodular 20%; Nodular-ulcerative: 24%; Flat-ulcerative; 19% and Plaque-like 5%. Lesion type in the ILMA group were: Nodular 24%; Nodular-ulcerative: 18%; Flat-ulcerative; 15% and Plaque-like 9%. Lesion site (% of lesions) in the IMMA group: Shoulder: 7; Upper arm: 11; lower arm: 14; Elbow: 1; Hand: 10; Thigh: 5; Knee: 4; Leg: 12 and Foot: 4. Lesion site (% of lesions) in the ILMA group: Shoulder: 5; Upper arm: 9; lower arm: 11; Elbow: 2; Hand: 8; Thigh: 7; Knee: 3; Leg: 12 and Foot: 9.<br>Incl: To have only a few (one to three) simple lesions, on a no-facial site; clinically confirmed CL by direct slit smears and/or in skin-punch biopsies of the active, infiltrated edge of a representative lesion.<br>Excl: multiple or disseminated lesions, lesions aged > six months, pregnancy, chronic illness, an immunologically compromised condition, hyper allergic reaction to the trial drugs, treatment with regular medications which may affect specific therapy, treatment with antileishmanial drugs within the previous six months, and the presence of scars of previously healed lesions.<br>*Leishmania* species: *L. major* in the area. |
| Interventions | T1: IMMA 15 mg/kg/d daily on 6 days/week up to 12 injections<br>n = 40. Total number of lesions: 77. MSL: 1.8 $cm^2$. MDLBT: 72.7 days.<br>T2: ILMA 0.2 to 0.8 ml/lesion every other day over a 30 day period or until lesion had blanched.<br>n = 40. Total number of lesions: 70. MSL: 1.2 $cm^2$. MDLBT: 67.9 days. |
| Outcomes | *Primary outcome*<br>Percentage of lesions 'cured' at the end of treatment<br>*Secondary outcomes*<br>Prevention of scarring<br>Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|

**Alkhawajah 1997** (*Continued*)

| | | |
|---|---|---|
| Blinding?<br>All outcomes | Yes | Single-blinded: One outcome assessor unaware of the treatment assessed lesions |
| Intention-to-treat/Drop-outs? | No | 13 out of 80 (< 25%) |

**Alrajhi 2002**

| | |
|---|---|
| Methods | FU: one year post-treatment<br>D: Randomised clinical trial |
| Participants | Saudi Arabia<br>n = 209 (145 completed the study)<br>Px from the area of Al-Ahsaa and Ryyadh regions of Saudi Arabia, Because of the criteria for inclusion and the limited number of women at risk for *leishmania* in the study areas, there was only one female Px. Most of the Px were foreign construction workers or farmers originally from countries where CL is not endemic. One of five Px was a local national.<br>Incl: age > 12 years, presence of lesions parasitologically confirmed leishmaniasis, and non-use of antileishmanial therapy during previous two months.<br>Excl: pregnancy, potential for pregnancy, breast feeding, the presence of lesions on the face or ears, the presence > 10 lesions, a history of liver disease, an elevated serum, creatinine concentration, abnormal results on liver-function tests, and allergy to fluconazole.<br>*Leishmania* species: *L. major* 56 Px (27%)<br>Compliance assessment: An independent observer evaluated the rates of compliance and side effects by interviewing Px and counting their remaining capsules. |
| Interventions | T1: Fluconazole orally 200 mg OD for 6 weeks<br>n = 106. MNL: 3.1. MSL: 17 mm. MDLBT: 9.2 weeks.<br>T2: Placebo 200 mg OD for 6 weeks<br>n = 103. MNL: 3.7. MSL: 19 mm. MDLBT: 7.7 weeks.<br>Co-treatment: SSG was offered during follow-up if oral therapy was considered to have failed (14 Px in the fluconazole group and 33 in the placebo group). |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' three months after treatment<br>*Secondary outcomes*<br>Speed of healing (time taken to be 'cured')<br>Adverse effects |
| Notes | Sample size: Large/ C |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | table of random numbers |

**Alrajhi 2002** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment? | Yes | Claimed that packages were coded |
| Blinding?<br>All outcomes | Yes | Double-blinded: Px, clinicians and outcome assessors |
| Intention-to-treat/Drop-outs? | Yes | 64 out of 209 (< 55%) |

**Alsaleh 1995**

| | |
|---|---|
| Methods | FU: six weeks<br>D: Randomised clinical trial |
| Participants | Kuwait<br>n = 33<br>PX with CL, with an age range from 14 to 66 years old. M/F: 26/7. The number of lesions ranged from one to eight. Site of the lesions in the ketoconazole 600 mg group: 46% on the upper extremities and 24/% on the lower extremities. In the Ketoconazole 800 mg: 58% on the upper extremities; 21% on the lower extremities and 21% on head and neck.<br>Incl: Only the smear-positive cases were included in the study.<br>Excl: Px < 14 years of age and pregnant nursing women.<br>*Leishmania* species not specified. |
| Interventions | T1: Ketoconazole 600 mg<br>n = 15 (n =1 8 ITT). MNL: 3.56 (range 2 to 8). MDLBT: 3.4 months (range 1.5 to 7).<br>T2: Ketoconazole 800 mg<br>n = 11(n = 15 ITT). MNL: 3.27 (range 1 to 6). MDLBT: 4.5 months (range 1 to 12).<br>Frequency: daily for sixweeks or until the Px was cured (whatever occurred earlier) |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' at the end of treatment<br>*Secondary outcomes*<br>Duration of remission and percentage of people with treated lesions that recur within six months<br>Adverse effects |
| Notes | Sample size: Small/ NC |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Blinding?<br>All outcomes | Unclear | no mention about blinding |
| Intention-to-treat/Drop-outs? | No | 7 out of 33 (< 25%) |

**Asilian 1995**

| | |
|---|---|
| Methods | FU: 105 days after starting treatment<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 251<br>Conducted in 8 primary health centres around Borkhar, north of Isfahan. M/ F: 131/120, mainly children. Site of lesions: 82 to 90 Px in the limb, 28 to 38 in the head and 7 to 9 in the trunk. Type of lesion: 12 to 17 Px had papular lesions; 12 to 16 nodular; 76 to 79 nodule-ulcerative; 11 to 12 flat-ulcerative and 13 to 20 plaque-like lesions.<br>Incl: two years or older with a single lesion that was parasitologically positive, < 5 cm in diameter, at least 3 cm from the eyes, and which had been present < 4 months.<br>Excl: if they were pregnant or nursing mothers, had been previously treated for leishmaniasis, had any known intercurrent illness or a history of allergy to aminoglycosides.<br>*Leishmania* species: Infections here were thought to be caused entirely by *L. major* parasites, although there is probably some *L. tropica* infection within the city of Isfahan. |
| Interventions | T1: PR (15% aminosidine and 10% urea) in petroleum ointment twice a day for 14 days.<br>n = 126. MNL: 1. MDLBT: 1.5 weeks.<br>T2: Placebo ointment TD for 14 days<br>n = 125. MNL: 1. MDLBT: < 4 weeks.<br>Additional treatment, usually parenteral antimony, was given if lesions were judged to have worsened (25 participants in the PR-treated group and 28 in the placebo group). |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' 2.5 months after treatment<br>*Secondary outcomes*<br>Adverse effects<br>*Tertiary outcomes*<br>Microbiological or histopathological cure of skin lesions |
| Notes | Sample size: Large/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | Randomisation of treatment was carried out in Geneva (Switzerland) but did not state how that was done. Identical ointment tubes were numbered and allocated to consecutive eligible Px. |
| Blinding?<br>All outcomes | Yes | Double-blinded: Px and the study team |
| Intention-to-treat/Drop-outs? | No | 16 out of 251 (10%) |

**Asilian 2003**

| | |
|---|---|
| Methods | FU: 105 days after starting treatment<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 233 (216 completed the study)<br>Three primary health centres around Borkhar district north of Isfahan. Baseline comparability: with regard to age, sex, ulcerated lesion, levels of haemoglobin and serum glutamic oxaloacetic transaminase.<br>Incl: Px with a single parasitologically confirmed lesion, < 5cm in diameter.<br>Excl: if their lesions had > 4 months, were aged < 2 years, were pregnant or nursing mothers, had been treated previously, or had any intercurrent illness or history of allergy to aminoglycosides.<br>*Leishmania* species: *L. major* |
| Interventions | T1: PR (aminosidine) ointment for four weeks<br>n = 117. MNL: 1.<br>T2: PR (aminosidine) ointment for two weeks followed by two weeks of paraffin<br>n = 116. MNL: 1.<br>Co-treatment: if lesions were bad enough, they were treated with antimoniate. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' 2.5 months after treatment<br>*Secondary outcomes*<br>Adverse effects<br>*Tertiary outcomes*<br>Microbiological or histopathological cure of skin lesions |
| Notes | Sample size: Large/C |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | computer-generated random number table |
| Blinding?<br>All outcomes | Yes | Double-blinded: Px and the clinical and parasitological evaluators. Tube ointments looked and smelled identical |
| Intention-to-treat/Drop-outs? | No | 87 out of 233 ( < 55%) |

**Asilian 2004A**

| | |
|---|---|
| Methods | FU: six months<br>D: Randomised clinical trial |

**Asilian 2004A** (*Continued*)

| | |
|---|---|
| Participants | Iran<br>n = 400 (370 completed the study)<br>Px age ranged from 2 to 65 years, M/F: 186/184.<br>Incl: confirmed diagnosis parasitologically and clinically. Lesions with a duration of < 8 weeks.<br>Excl: Px with a history of >8 weeks, those with allergy to antimonials, and lactating or pregnant women.<br>*Leishmania* but species not declared. |
| Interventions | T1: Combined cryotherapy and ILMA<br>n = 100. Total number of lesions: 149.<br>T2: Cryotherapy alone<br>n = 200. Total number of lesions: 230.<br>T3: ILMA alone<br>n =100. Total number of lesions: 160.<br>Frequency: fortnightly until complete cure or for up to six weeks. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' at the end treatment<br>*Secondary outcomes*<br>Duration of remission and percentage of people with treated lesions that recur within six months<br>Adverse effects<br>*Tertiary outcomes*<br>Microbiological or histopathological cure of skin lesions |
| Notes | Sample size: Large/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Unclear | no mention about blinding |
| Intention-to-treat/Drop-outs? | No | 30 out of 400 ( < 10%) |

**Asilian 2004B**

| | |
|---|---|
| Methods | FU: 24 weeks<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 233<br>M/F: 55/68 with 183 lesions were included in the $CO_2$ laser group. M/F: 40/70 with 250 lesions in the MA group. The age of Px ranged from 12 to 60 years. In 47% of cases, Px had one lesion |

**Asilian 2004B** (*Continued*)

| | |
|---|---|
| | and in 53% of cases they had 2 to 5 lesions. There were more lesions on the upper limbs (43%), and lesions were < 5 $cm^2$. In the remaining, the lesion duration was two to four months.<br>Incl: age 7 to 70 years; disease confirmed clinically and by laboratory methods; lesions present; and surface area of lesions $\leq$5 $cm^2$.<br>Excl: Disease duration > 4 months; pregnancy or breast feeding; chronic disease; immune suppression; and sporotrichoid forms.<br>*Leishmania* species: not reported. |
| Interventions | T1: $CO_2$ laser (30 W, continuous) was applied to the lesion and an area 2 to 3 mm around it. This procedure was repeated until the ulcer bed turned brown. After completion of the procedure, the ulcer was covered with 2% erythromycin ointment.<br>n = 123. Mean number of lesions : 1.49.<br>T2: IMMA 50 mg/kg/d for 15 days and after 15 days of rest, this treatment was repeated.<br>n = 110. Mean number of lesions : 2.27. |
| Outcomes | *Primary outcome*<br>Percentage of lesions 'cured' 1.5 months after treatment<br>*Secondary outcomes*<br>Speed of healing (time taken to be 'cured')<br>Prevention of scarring<br>Adverse effects |
| Notes | Sample size: Large/NC |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Adequate sequence generation? | Yes | author contacted: coin flip method |
| Blinding?<br>All outcomes | Unclear | no mention about blinding |
| Intention-to-treat/Drop-outs? | No | 59 out of 233 ( < 55%) |

**Asilian 2006**

| | |
|---|---|
| Methods | FU: two months<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 60 (57 completed the study)<br>M/F 26/3. Age range from 5 to 59 years. The most common sites of lesions (<10) were on the extremities.<br>Incl: confirmation of typical CL by positive Giemsa-stained direct smear for Leishman-Donovan bodies. |

**Asilian 2006** (*Continued*)

| | |
|---|---|
| | Excl: > 2 lesions or lesions with > 20 mm induration diameter, duration of the disease > 2 months, previous use of any anti-leishmanial treatments, pregnant or nursing women, children < 5 years of age, serious concomitant medical problems, history of seizure, and photosensitivity.<br>*Leishmania* species: *L. major* |
| Interventions | T1: PDT ( 10% 5-aminolevulinic acid (5-ALA) hydrochloride in a water-in-oil cream was applied topically). Lesions irradiated using visible red light at 100J/ $cm^2$ per treatment session, repeated weekly for four weeks.<br>n = 20/20. Total number of lesions 31. MNL: 1.55. MDLBT: 38 days.<br>T2: PR (15% PR sulfate plus 12% MBCL) in a soft white paraffin-based ointment applied topically TD at 1 mm thickness over the total surface of the lesion(s) for 28 days.<br>n = 19/20. Total number of lesions: 34. MNL: 1.75. MDLBT: 35 days.<br>T3: Placebo applied topically TD at 1 mm thickness over the total surface of the lesion(s) for 28 days.<br>n = 18/20. Total number of lesions: 30. MNL: 1.65. MDLBT: 36 days. |
| Outcomes | *Primary outcome*<br>Percentage of lesions 'cured' two months after treatment<br>*Secondary outcomes*<br>Prevention of scarring<br>Adverse effects<br>*Tertiary outcomes*<br>Microbiological or histopathological cure of skin lesions |
| Notes | Sample size: Medium/C |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | computer-generated random number table |
| Blinding?<br>All outcomes | Yes | Double-blinded: Px and clinicians (however, one arm was not blind (PDT group)) |
| Intention-to-treat/Drop-outs? | No | 3 out of 60 ( < 10%) |

**Ben- Salah 1995**

| | |
|---|---|
| Methods | FU: 105 days<br>D: Randomised clinical trial |

**Ben- Salah 1995** (*Continued*)

| | |
|---|---|
| Participants | Tunisia<br>n = 132 (115 completed the study)<br>Carried out at Sidi- Bouzid. The site of lesions were mainly found in the upper and lower limbs, and trunk and face also. They were papular, nodular and nodule-ulcerative type of lesions. Baseline comparability: with regard to age, sex, location and severity of the lesion.<br>Incl: Px aged 2 to 60 years old, with a single lesion diagnosed by the presence of parasite in stained dermal smears. Px reported that they had not received any prior anti-leishmanial treatment.<br>Excl: known allergy, adverse reactions to aminoglycoside antibiotics, multiple lesions, an active lesion measuring > 5cm in diameter, or if their ulcerated lesion had already persisted for more than four months, lesions < 3 cm from the eye, or who by the physician's judgment required systemic antimonial treatment: participants with serious concomitant diseases; Px under medication for other illnesses likely to interfere with this study; and pregnant women or nursing mothers.<br>*Leishmania* species: *L. major* |
| Interventions | T1: 15% PR and 10% urea in soft white paraffin ointment<br>n = 57 (66 ITT). MNL: 1. MSL: 22.1 mm. MDLBT: 5.67 weeks.<br>T2: Placebo ointment (10% urea in soft white paraffin)<br>n = 58 (66 ITT). MNL: 1. MSL: 23 mm. MDLBT: 4.78 weeks.<br>Frequency: TD for 14 days |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' 2.5 months after treatment initiation (105 days)<br>*Secondary outcomes*<br>Adverse effects |
| Notes | Sample size: Medium/C |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | Tubes containing drug or placebo were randomly numbered, and were given in numerical order to Px as they were admitted to the study |
| Allocation concealment? | Yes | The code remained unknown to Px and investigators until the study had been completed |
| Blinding?<br>All outcomes | Yes | Double-blinded: Px and clinicians |
| Intention-to-treat/Drop-outs? | No | 17 out of 132 ( < 25%) |

**Dandashi 2005**

| | |
|---|---|
| Methods | FU: not reported<br>D: Randomised clinical trial |
| Participants | Allepo-Syria<br>n = 79 (only 65 completed the study)<br>Baseline comparability: not mentioned.<br>*Leishmania* species: *L. tropica*. |
| Interventions | T1: Fluconazole orally 200 mg/d for 6 weeks.<br>n = 46. Total number of lesions: 264.<br>T2: Placebo orally for six weeks.<br>n = 19. Total number of lesions: 102. |
| Outcomes | *Primary outcome*<br>Percentage of lesions 'cured' (FU not reported)<br>*Secondary outcomes*<br>Adverse effects |
| Notes | This is an abstract<br>Sample size: Medium/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Yes | Double-blinded: only stated but not reported who was blinded |
| Intention-to-treat/Drop-outs? | No | 14 out of 79 ( < 25%) |

**Dogra 1990**

| | |
|---|---|
| Methods | FU: six weeks. But three months for relapses assessment.<br>D: Randomised clinical trial |
| Participants | India<br>n = 20<br>Px with CL with single or multiple lesions, the duration of the lesions varied from 4 to 16 weeks. The ages of Px ranged from 14 to 56 years. Baseline comparability: not clearly comparable, because no information is given about the control group.<br>Incl: Px with CL confirmed by the presence of LT bodies in the slit skin smear stained with Leishman stain.<br>Excl: Women of child-bearing age.<br>*Leishmania* species: *L. tropic*a in the area. |

**Dogra 1990** (*Continued*)

| | |
|---|---|
| Interventions | T1: Itraconazole orally 4 mg/kg per day for 6 weeks (max. of 200 mg)<br>n = 15 . MNL: 2. MDLBT: 9 weeks.<br>T2: Control group (No treatment)<br>n = 5 |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' at the end of treatment<br>*Secondary outcomes*<br>Duration of remission and percentage of people with treated lesions that recur within three months.<br>Adverse effects<br>*Tertiary outcomes*<br>Microbiological or histopathological cure of skin lesions: |
| Notes | Sample size: Small/NC |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Adequate sequence generation? | Unclear | Proportion of 2 to 4:1 |
| Blinding?<br>All outcomes | No | |
| Intention-to-treat/Drop-outs? | Yes | ND |

**Dogra 1991**

| | |
|---|---|
| Methods | FU: six weeks<br>D: Randomised clinical trial |
| Participants | India<br>n = 120<br>Px's age ranged from 15 to 56 years, M/F: 52/68. The duration of the lesions ranged from three weeks to three months. Lesions were situated mainly on the exposed parts of the body (face, arms and feet). Forty-six Px had a single lesion while 74 Px had multiple lesions (maximum 13). Baseline comparability: mentioned but not shown: no statistical difference between both groups.<br>Incl: demonstration of *Leishmania* from skin lesion by the slit smear technique.<br>Excl: pregnant women and children < 12 years old, Px suffering from any chronic illness; immuno-compromised and those known to be allergic to sulphones; prior therapy for CL in any form; Px with scars of healed leishmanial lesions; lesions of > 4 months duration.<br>*Leishmania* species: *L. tropic*a in the area. |

**Dogra 1991** (*Continued*)

| | |
|---|---|
| Interventions | T1: Dapsone tablets (100 mg)<br>n = 60. 24/60 had single lesions.<br>T2: Placebo tablets<br>n = 60. 22/60 had single lesions.<br>Frequency: every 12 h for 6 weeks.<br>Co-treatment: no topical medication was prescribed except for wound hygiene. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' at the end of treatment<br>*Secondary outcomes*<br>Adverse effects<br>*Tertiary outcomes*<br>Microbiological or histopathological cure of skin lesions |
| Notes | Sample size: Medium/C |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Yes | Double-blind: only stated but not reported who was blinded. Tablets were identical in appearance |
| Intention-to-treat/Drop-outs? | Yes | ND |

**Dogra 1992**

| | |
|---|---|
| Methods | FU: six weeks. But three months for assessment of relapses.<br>D: Randomised clinical trial |
| Participants | India<br>n = 60<br>Sex not mentioned. Eight, 11 and 12 Px had multiple lesions in the itraconazole, dapsone and placebo groups respectively. Baseline comparability: not mentioned.<br>Incl: Px with localised CL and only smear positive cases.<br>Excl: not being smear positive.<br>*Leishmania* species: *L. tropica* in the area. |
| Interventions | T1: Itraconazole 4 mg/kg/d (max. 200 mg) for 6 weeks<br>n = 20<br>T2: Dapsone 4 mg /kg in 2 doses/d for 6 weeks<br>n = 20<br>T3: Placebo control group<br>n = 20 |

**Dogra 1992** (*Continued*)

| | |
|---|---|
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' at the end of treatment<br>*Secondary outcomes*<br>Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Unclear | no mention about blinding |
| Intention-to-treat/Drop-outs? | Yes | ND |

**Dogra 1996**

| | |
|---|---|
| Methods | FU: three months<br>D: Randomised clinical trial |
| Participants | India<br>n = 20<br>The age of the Px ranged from 19 to 62 years, M/F: 15/5. The duration of the lesions ranged from 2 weeks to 16 weeks, they were mainly seen on exposed parts of the body. Nine had a single lesion and 11 Px had a multiple lesion. Baseline comparability: not mentioned.<br>Incl: Px with localised CL. Demonstration of parasites from skin lesions by slit smear examination.<br>Excl: Women of child-bearing age and children < 18 years old. Px suffering from any chronic illness; immunocompromised Px; prior therapy for CLs in any form; scars of healed leishmanial lesions; lesions of four months or more duration and Px showing abnormality in liver function tests.<br>*Leishmania* species: *L. tropica* in the area. |
| Interventions | T1: Itraconazole orally (two 100 mg capsules) for 6 weeks<br>n = 10. 4/10 participants had single lesions.<br>T2: Placebo orally (two capsules) for six weeks<br>n = 10. 5/10 participants had single lesions.<br>Frequency: OD for six weeks. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' three months after treatment<br>*Secondary outcomes*<br>Adverse effects<br>*Tertiary outcomes*<br>Microbiological or histopathological cure of skin lesions |

**Dogra 1996** (*Continued*)

| | |
|---|---|
| Notes | Sample size: Small/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Yes | Double-blind: Px and outcome assessors |
| Intention-to-treat/Drop-outs? | Yes | ND |

**Esfandiarpour 2002**

| | |
|---|---|
| Methods | FU: one month<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 150<br>M/F: 69 /81 with typical CL and an average duration of symptoms of 8 months. Mean age 14 years. Range of number of lesions: one to seven. The common sites of involvement were the face and extremities. By groups were as follows: Oral AL: face: 62%; upper limbs: 34%; lower limbs: 4% and trunk: nil. MA: face: 48%; upper limbs: 38%; lower limbs: 14% and trunk: nil. AL + MA: face: 78%; upper limbs: 15%; lower limbs: 6% and trunk: 2%. The majority of Px had plaque-type, papular and nodular lesions. By groups: AL: plaque: 64%; papule: 29% and nodule: 7%. MA: plaque: 71%; papule: 18% and nodule: 11%. AL + MA: plaque: 77%; papule: 19% and nodule: 4%.<br>Incl: Positive direct smear or documented skin biopsy; not pregnant or nursing at the time of therapy; no serious systemic illness; no sensitivity to antimonial drugs or AL<br>Excl: Not having received treatment for at least two months before entry into the study.<br>*Leishmania* species: *L. tropica* in the area. |
| Interventions | T1: AL orally 15 mg/kg/d for 3 weeks<br>n = 50. Mean number of lesions: 1.5. Mean duration of disease before therapy: eight months.<br>T2: IMMA 30 mg/kg/d for 2 weeks<br>n = 50. Mean number of lesions: 1.8. Mean duration of disease before therapy: 7.4 months.<br>T3: AL + IMMA simultaneously<br>n = 50. Mean number of lesions: 1.4. Mean duration of disease before therapy: eight months. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' at the end of treatment<br>*Secondary outcomes*<br>Quality of life<br>Adverse effects |
| Notes | Sample size: Medium/NC |

**Esfandiarpour 2002** (*Continued*)

| ***Risk of bias*** | | |
|---|---|---|
| **Item** | **Authors' judgement** | **Description** |
| Blinding?<br>All outcomes | Unclear | no mention about blinding |
| Intention-to-treat/Drop-outs? | Yes | ND |

**Faghihi 2003**

| | |
|---|---|
| Methods | FU: one year<br>D: Randomised clinical trial |
| Participants | Isfahan (Iran)<br>n = 96<br>M/F: 40/56 with an age range 1 to 48 (mean age of 16 years old and a median of 14.5 years). All lesions treated were papules or early nodules with mean diameter of about 4 mm. Baseline comparability: they were then stratified by sex and number of lesions and were recruited for the trial.<br>Incl: Px with a clinical and parasitological diagnosis of CL.<br>Excl: pregnant or had > 3 lesions, ulcerative lesions, lesions with cartilage or lymphatic involvement or hypersensitivity to the drug.<br>*Leishmania* species: *L. major* is endemic in Isfahan. |
| Interventions | T1: 15% PR sulphate and 10 % urea in Eucerin ointment, applied TD at 1 mm thickness over the total surface of the lesion(s) during a maximum of 3 months.<br>n = 48. Mean number of lesions per person: one.<br>T2: ILMA injections of 1.5 g/5 mL (maximum 12), weekly. The mean amount of solution required for each lesion was 0.2 to 0.8 mL.<br>n = 48. Mean number of lesions per person: one. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' within two months after treatment<br>*Secondary outcomes*<br>Duration of remission and percentage of people with treated lesions that recur within one year<br>Prevention of scarring |
| Notes | Sample size: Medium/C |

| ***Risk of bias*** | | |
|---|---|---|
| **Item** | **Authors' judgement** | **Description** |

**Faghihi 2003** (*Continued*)

| | | |
|---|---|---|
| Adequate sequence generation? | Yes | stratified blocked randomisation method |
| Blinding?<br>All outcomes | Unclear | no mention about blinding |
| Intention-to-treat/Drop-outs? | Yes | ND |

**Firooz 2005**

| | |
|---|---|
| Methods | FU: five weeks<br>D: Randomised clinical trial |
| Participants | Isfahan (Iran)<br>n = 72<br>M/F: 33/39. Mean age 20.2. (SD 9.6). Baseline comparability: regarding age, sex and location of the lesions.<br>Incl: the presence of parasitologically confirmed lesion(s) of CL, age between 12 and 60 years, and otherwise healthy on the basis of medical history and physical examination.<br>Excl: women of child-bearing age without adequate effective contraception, pregnant or breast feeding, duration of lesions > 8 weeks, the presence of lesions on face, joints or near the mucous membranes, the presence of > 5 lesions or any lesion with a diameter > 5 cm, and history of any antileishmanial therapy in the past 4 weeks.<br>*Leishmania* species: *L. major* endemic in the area. |
| Interventions | T1: IL 2% zinc sulphate (Zn $SO_4$)<br>n = 36. MNL: 1.4. MSL: 7.6 mm. MDLBT: 5.8 weeks.<br>T2: ILMA<br>n = 36. MNL: 1.5. MSL: 7.9 mm. MDLBT: 5.5 weeks.<br>Frequency: up to six weeks. |
| Outcomes | *Primary outcome*<br>Percentage of lesions 'cured' five weeks after treatment<br>*Secondary outcomes*<br>Adverse effects |
| Notes | The plot and the figures were not matched accordingly<br>Sample size: Medium/NC |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Adequate sequence generation? | Yes | table of random numbers |

**Firooz 2005** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment? | Yes | The randomisation sequence was concealed from the investigators until the data entry was completed and the data bank was locked |
| Blinding?<br>All outcomes | Yes | Double-blind: Px and investigators |
| Intention-to-treat/Drop-outs? | Yes | 37 out of 72 ( < 55%) |

**Firooz 2006**

| | |
|---|---|
| Methods | FU: 20 weeks after initiation of treatment<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 119<br>In the city of Mashad in the Khorasan Razavi province in northeast Iran. Px were recruited among Px with CL who were referred to two primary care health clinics established by the Undersecretary of Public Health as the Mashad University of Medical Sciences, aged approximately 27 years and approximately 50 to 55% of the Px were female (35/59 in the imiquimod group, and 31/60 in the placebo group). Lesions were mainly located on the upper extremities (66.3%), and around 15 to 17% on the face and lower extremities. The number of lesions were 128 and 124 in the imiquimod and placebo groups respectively.<br>Incl: Parasitologically proven cases of CL based on positive smear or culture, otherwise healthy participants, age 12 to 60 years.<br>Excl: Pregnant or lacting women, duration of the lesions > 6 months, number of lesions > 6 months, number of lesions > 5, any lesions > 5 cm, history of any standard course of treatment with antimonials, history of allergy to antimonials, serious systemic illnesses, and participation in any drug trials in the last 60 days.<br>*Leishmania* species: *L. tropica* endemic in the area.<br>Compliance assessment: The pharmacist evaluated the compliance by counting the remaining sachets of imiquimod. |
| Interventions | T1: Imiquimod cream 5% plus IMMA<br>n = 59. Mean number of lesions: 2.2. Mean duration of the disease: 13 weeks. Mean size of lesions: 174 $mm^2$.<br>T2: Placebo cream plus IMMA<br>n = 60. Mean number of lesions: 2.0. Mean duration of the disease: 13.2 weeks. Mean size of lesions: 237 $mm^2$.<br>Frequency: imiquimod and placebo 3 times per week for 28 days, IMMA 20 mg/kg/d for 14 days |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' 3.5 months after treatment<br>*Secondary outcomes*<br>Duration of remission and percentage of people with treated lesions that recur within six months<br>Adverse effects |

**Firooz 2006** (*Continued*)

| | | |
|---|---|---|
| Notes | Sample size: Medium/C | |
| ***Risk of bias*** | | |
| **Item** | **Authors' judgement** | **Description** |
| Adequate sequence generation? | Yes | stratified blocked randomisation method |
| Allocation concealment? | Yes | The randomisation allocation concealment was performed by sending the randomisation numbers in envelopes to a pharmacist who was responsible for giving the assigned treatment after each eligible Px was enrolled |
| Blinding?<br>All outcomes | Yes | Single-blind (the outcome assessors were unaware of the drugs used by the Px) |
| Intention-to-treat/Drop-outs? | Yes | 30 out of 119 ( < 55%) |

**Gholami 2000**

| | |
|---|---|
| Methods | FU: 60 days (after the 3 week treatment, Px were followed for another period of 40 days)<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 197 (171 completed the study)<br>M/F: 51/45 with mean age of 18.5 years were treated with garlic cream and M/F: 38/37 with mean age of 23.7 years were treated with placebo. Baseline comparability: regarding age, sex, duration of lesion, type, and size of lesion.<br>Incl: CL confirmed with direct smear, age 5 to 50 years, maximum number of lesions 3, duration of disease < 100 days.<br>Excl: previous treatment for leishmaniasis, use of immunosuppressives, history of chronic systemic disease, lesions on face, pregnancy or lactating, age < 5 years and duration of disease > 100 days.<br>*Leishmania* species: *L. major*. |
| Interventions | T1: Garlic cream 5%<br>n = 96<br>T2: Placebo<br>n = 75<br>Frequency: Both applied TD under occlusion with sterile gauze for 3 hours, for 20 days. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' one month (40 days) after treatment |

**Gholami 2000** (*Continued*)

| | |
|---|---|
| Notes | We only have the abstract. The author (A. Khamesipour) was contacted and kindly agreed to extract the data from the original paper written in Persian.<br>Sample size: Large/C |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | List generated by a computer |
| Blinding?<br>All outcomes | Yes | Double-blind: Px, clinicians and outcome assessors |
| Intention-to-treat/Drop-outs? | No | 26 out of 197 ( < 25%) |

**Harms 1991**

| | |
|---|---|
| Methods | FU: ten weeks<br>D: Randomised clinical trial |
| Participants | Syria<br>n = 40<br>In the outpatient clinic of the department of Dermatology, Aleppo, Syria. M/F: 17/23, and their age range went from 6 to 60 years old. Type of lesions (%) in MA group: papular: 13; papular-nodular: 21; nodular-ulcerative: 61; plaque-form: 5. Lesion site (%) in glucantime group: upper extremity: 63; lower extremity: 18; face: 18; trunk: none. Type of lesions (%) in IFN-$\gamma$ group: papular: 19; papular-nodular: 19; nodular-ulcerative: 62; plaque-form: none. Lesion site (%) in IFN-$\gamma$ group: upper extremity: 59; lower extremity: 30; face: 8; trunk: 3.<br>Incl: Up to 3 lesions diagnosed clinically and parasitologically as CL; absence of chronic or intercurrent systemic disease.<br>Excl: Pregnancy and no prior antimonial medication.<br>*Leishmania* species: *L. tropica* |
| Interventions | T1: ILMA (1 to 3 ml)<br>n = 20 with 38 lesions. MSL: 15 x 14 mm (4 x 4- 49 x 42). MDLBT: 2.5 months (1 to 6).<br>T2: IL Lyophilised recombinant IFN-$\gamma$ (25 mg)<br>n = 20 with 37 lesions. MSL: 13 x 11 mm (7 x 7- 45 x 40). MDLBT: 2.5 months (2 to 8).<br>Frequency: once weekly for five weeks |
| Outcomes | *Primary outcome*<br>Percentage of lesions 'cured' one month after treatment<br>*Secondary outcomes*<br>Adverse effects<br>*Tertiary outcomes*<br>Microbiological or histopathological cure of skin lesions |

**Harms 1991** (*Continued*)

| | |
|---|---|
| Notes | Sample size: Small/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | Random numbers table |
| Blinding?<br>All outcomes | Unclear | blinding not mentioned |
| Intention-to-treat/Drop-outs? | Yes | ND |

**Iraji 2004**

| | |
|---|---|
| Methods | FU: six weeks<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 104 (66 completed the study)<br>Study carried out in the Department of Dermatology, Isfahan Medical University. M/F: 50/54, and their age range went from 2 to 67 years old.<br>Incl: Px with proven leishmaniasis based on typical lesions of ACL and a positive direct smear. Number of lesions < 4 and duration of lesion < 12 weeks.<br>Excl: Cases of reinfection, pregnant or nursing women, those who had lesion on the face or joints and Px with sporotrichoid or erysipeloid lesions.<br>*Leishmania* species: Due to a previous study in the area, it was likely that Px were infected with *L. major*. |
| Interventions | T1: ILMA injection of 50ml.<br>n = 35 (ITT 55). MDLBT: 6.73 weeks<br>T2: IL ZS injection of 50 ml.<br>n = 31 (ITT 49). MDLBT: 7.64 weeks.<br>In cases were there was a slight to mild improvement, another injection was given after two weeks. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' at the end of treatment<br>*Secondary outcomes*<br>Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

**Iraji 2004** (*Continued*)

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Yes | Double-blind: only stated but not reported who was blinded. The vials were similar and marked A or B by an independent physician |
| Intention-to-treat/Drop-outs? | No | 38 out of 104 (< 55%) |

**Iraji 2005**

| | |
|---|---|
| Methods | FU: For clinical and parasitological follow-up on day 30 and for only parasitological follow-up on day 60.<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 80 (65 completed the study)<br>M/F: 33/32, and their age range went from 8 to 55 years old.<br>Incl: Had the clinical signs of CL and all of their cutaneous lesions were found smear-positive for amastigotes.<br>Excl: Cases who had first noticed a skin lesion > 3 months previously, had lesions on their face, had lesions with diameter of > 3 cm, had received previous treatment, or who were lactating or pregnant.<br>*Leishmania* species: *L. tropica* and *L. major* are responsible for hyperendemic CL in rural areas and endemic CL in parts of many cities in Iran. |
| Interventions | T1: PR sulphate 15% + 10% urea applied to a 1 mm-thick layer<br>n = 30/40. MDLBT: 1.65 years.<br>T2: Placebo group (Eucerin containing 10% urea) applied topically<br>n = 35/40. MDLBT 1.75 years.<br>Frequency: TD for 30 days. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' one month after treatment<br>*Secondary outcomes*<br>Adverse effects |
| Notes | Sample size: Medium/C |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | Computer-based randomisation |
| Blinding?<br>All outcomes | Yes | Double-blind: only stated but not reported who was blinded |

**Iraji 2005** (*Continued*)

| | | |
|---|---|---|
| Intention-to-treat/Drop-outs? | No | 15 out of 80 (< 25%) |

**Jaffar 2006**

| | |
|---|---|
| Methods | FU: three months<br>D: Randomised clinical trial |
| Participants | Saudi Arabia (Barhain)<br>n = 62<br>Their ages ranged between 3 to 65 years with a mean age of 20 years. The duration of the lesions varied between 1 and 12 months (mean 2.6 months). The lesions of CL were single or multiple and were mostly over the extremities (upper limbs 51% and lower limbs 38%) and to a lesser extent on the face 30%. Most of the lesions were active being nodular, nodule-ulcerative, or ulcerative. Two of the Px were members of the same family. However, the rest of the Px had a negative family history. Also, 2 groups were analysed; group I (children from 3 to 11 years of age - mean age, 7.5), and group II (adults from 12 to 65 years - mean age, 33). 32 Px enrolled in group I and 30 in group II. Out of these 8 Px in each group (16 in total) served as control to receive the placebo.<br>Incl: Proved positive for leishmania parasites (amastigotes) on microscopic examination or biopsy.<br>*Leishmania* species: not reported. |
| Interventions | T1: Rifampicin orally in a dose of 10 mg/kg/d<br>n = 46.<br>T2: Placebo<br>n = 16.<br>Frequency: two equally divided doses during meals for four to six weeks |
| Outcomes | Primary outcome<br>Percentage of Px 'cured' three months after treatment<br>Secondary outcomes<br>Duration of remission and percentage of people with treated lesions that recur up to three months FU<br>Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Blinding?<br>All outcomes | Yes | Double-blind: only stated but not reported who was blinded. Capsules were identical in shape and colour |
| Intention-to-treat/Drop-outs? | Yes | 21 out of 62 (< 55%) |

**Kochar 2000**

| | |
|---|---|
| Methods | FU: 4 weeks<br>D: Randomised clinical trial |
| Participants | India<br>n =50 (46 completed the study)<br>Rifampicin versus placebo group regarding type of lesions in percentages were ulcerative 21.7 *versus* 17.4, nodular: 30.4 *versus* 30.4; nodule-ulcerative: 17.4 *versus* 30.4 and erythematous plaques : 30.4 *versus* 21.7. Regarding the distribution: face: 17.5 *versus* 20.9; neck; 3.5 *versus* 0; shoulder: 1.75 *versus* 0; arms: 17.5 *versus* 20.9; hand: 19.2 *versus* 18.6; legs; 28 *versus* 16.2; feet: 8.77 *versus* 20.9 and abdomen: 3.5 *versus* 2.32.<br>No mention about inclusion or exclusion criteria.<br>*Leishmania* species: *L. tropica* |
| Interventions | T1: Rifampicin 1200 mg/day orally<br>n = 23 (ITT n = 25). MNL: 2. MSL: 30 mm. MDLBT: 1.75 months.<br>T2: Placebo capsules orally<br>n = 23 (ITT n = 25). MNL: 2. MSL: 40 mm. MDLBT: 2 months.<br>Frequency: two divided doses for four weeks. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' at the end of treatment<br>*Secondary outcomes*<br>Adverse effects<br>*Tertiary outcomes*<br>Microbiological or histopathological cure of skin lesions |
| Notes | Sample size: Small/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Yes | Double-blind: Px and clinicians (data was collected on special proforma and kept double-blind). Tubes were identical in appearance |
| Intention-to-treat/Drop-outs? | No | 4 out of 50 (< 10%) |

**Kochar 2006**

| | |
|---|---|
| Methods | FU: six weeks<br>D: Randomised clinical trial |

**Kochar 2006** (*Continued*)

| | |
|---|---|
| Participants | India<br>n = 50<br>Hospital, Bikaner. M/F: 34/16. Male predominance was probably due to the habit of sleeping in open spaces outside the house without mosquito nets and improper clothing during night when the sandflies are active. Regarding the type lesion, erythematous nodular was the most common type (40%) followed by erythematous plaque (16%), erythematous ulcerative (14%), nodular (12%), ulcerative (10%) and nodular ulcerative (8%). Most cases were presented with one to three months of duration of the disease.<br>Incl: Px with a confirmed diagnosis of anthroponotic CL.<br>*Leishmania* species: *L. tropica* |
| Interventions | T1: Rifampicin (1200 mg/day) in two divided doses plus omeprazole 20 mg for 6 weeks<br>n = 25.<br>T2: Placebo for six weeks<br>n = 25. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' at the end of treatment |
| Notes | Sample size: Small/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Yes | Double-blind: Px and clinicians (data was collected on special proforma and kept double-blind) |
| Intention-to-treat/Drop-outs? | No | 6 out of 50 (< 25%) |

**Larbi 1995**

| | |
|---|---|
| Methods | FU: 30 days<br>D: Randomised clinical trial |
| Participants | Saudi Arabia<br>n = 58 (54 completed the study)<br>M/F: 42/12. Age range was 1 to 52. In the 2% miconazole group lesion types were nodular 34%, nodulo-ulcerative 59% and papular 7% and distributed in the lower limbs 56%; upper limbs 39%; head, neck, upper chest 5%. In the 1% clotrimazole group lesion types were nodular 41%, nodulo-ulcerative 56% and papular 3% and distributed in the lower limbs 34%; upper limbs 46%; head, neck, upper chest 19%, abdomen and groin 1%.<br>Incl: only Px in whom parasites (amastigotes) were demonstrated were enrolled.<br>Excl: pregnancy, chronic illness, immunocompromised or hyperallergic reaction to the trial drugs, treatment with regular medications such as antituberculous agents and steroids, which might have |

**Larbi 1995** (*Continued*)

| | |
|---|---|
| | affected specific therapy, treatment with anti-leishmanial drugs within the previous months, and the presence of scars of previously treated lesions.<br>*Leishmania* species: *L. major*<br>Compliance assessed: They were asked to bring all used and unused tubes of medication for inspection at the two-week follow-up visit. |
| Interventions | T1: 2% miconazole cream<br>n = 27. Total number of lesions: 62. MNL: Saudi: 2.2 and non-Saudi 3.4. MSL: 1.02 cm. MDLBT: 2.1 weeks.<br>T2: 1% clotrimazole cream<br>n = 31. Total number of lesions: 89. MNL: Saudi: 2.3 and non-Saudi 3.5.MSL: 1.38 cm. MDLBT: 2.3 weeks.<br>Frequency: TD for 30 consecutive days. |
| Outcomes | *Primary outcome*<br>Percentage of lesions 'cured' at the end of treatment<br>*Secondary outcomes*<br>*A*dverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | Table of random numbers |
| Blinding?<br>All outcomes | Yes | Double-blind: Px and clinicians. Tubes were not labelled |
| Intention-to-treat/Drop-outs? | No | 4 out of 58 ( < 10%) |

**Lynen 1992**

| | |
|---|---|
| Methods | FU: one month<br>D: Randomised clinical trial |
| Participants | Sudan<br>n = 70 (62 completed the study)<br>School children with CL. Baseline comparability: with regard to sex, age, number, size, duration and localization of ulcer, and previous treatment taken.<br>Incl: all positive smears.<br>Excl: children who had received diminazene aceturate or having been treated in hospital before were excluded. Even though many of the children had received previous treatment.<br>*Leishmania* specie not specified but *L. major* was presumed to be the causative parasite. |

**Lynen 1992** (*Continued*)

| | |
|---|---|
| | Compliance was calculated as the total number of applications given in each group divided by the number of days that Px had been under treatment (64.5% and 65.56% were the percentages in the Berelin and in the Savlon group respectively). |
| Interventions | T1: Berelin (1.05 g diminazene aceturate in 2.36 g of granulate, dissolved in 12.5 cc of distilled water) daily except on Fridays for 50 days<br>n = 32 (ITT n =3 5). MSL: < 20 mm was 58% (19/33) and > 20 mm 42% (14/33). MDLBT: 2 months or less was 52% (17/33) and > 2 months 48% (16/33).<br>T2: Savlon (cetrimide 15% plus chlorhexidine 1.5% in a 2% solution) for 50 days<br>n = 30 (ITT n = 35). MSL: < 20 mm was 61% (20/33) and > 20 mm 39% (13/33). MDLBT: 2 months or less was 64% (21/33) and > 2 months 36% (12/33). |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' at the end of treatment<br>*Secondary outcomes*<br>Duration of remission and percentage of people with treated lesions that recur 20 to 35 days after cure<br>Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | No | A double-blind study design was attempted, but could not be sustained as Savlon is a well known product and soapy on application |
| Intention-to-treat/Drop-outs? | No | 8 out of 70 (<2 5%) |

**Mashood 2001**

| | |
|---|---|
| Methods | FU: three months<br>D: Randomised clinical trial |
| Participants | Pakistan<br>n = 40<br>Px were army personnel who suffered from CL when they visited various endemic areas of Balochistan province. The center of the trial was the skin department of PNS Shifa, a naval hospital in Karachi. All the 40 Px were men. The age ranged between 20 and 40 years. Nodular, ulcerative and crusted forms were the most common morphological patterns seen. The majority of lesions were on hands and feet.<br>Incl: Not to have received any treatment before for their skin disease. |

**Mashood 2001** (*Continued*)

| | |
|---|---|
| | Excl: Very young and very old Px, those who had received some treatment for the disease, the Px suffering from diffuse CL or leishmaniasis recidivans and Px with some known cardiac, renal or hepatic disease.<br>*Leishmania* species not mentioned. |
| Interventions | T1: Oral AL 20 mg/kg/day in 3 to 4 divided doses tablet for 15 days<br>n = 20. MSL: 570.7 $mm^2$. MDLBT: 8.6 weeks (4 to 20).<br>T2: IV SSG 20 mg /kg/day I/V for 15 days<br>n = 20. MSL: 960.3 $mm^2$. MDLBT: 12.6 weeks (8 to 24). |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' at the end of treatment<br>*Secondary outcomes*<br>Adverse effects |
| Notes | Sample size: Small/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Unclear | blinding not mentioned |
| Intention-to-treat/Drop-outs? | Yes | ND |

**Mohebali 2007**

| | |
|---|---|
| Methods | FU: six months<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 63<br>Px lived in Golestan province, in the north-east of Iran. In average, Px were 20.2 years old in the miltefosine group, and 16.8 years old in the MA group. M/F: 35/28. Less than 20% of lesions were located on the face in each group, the rest were located on other sites of the body.<br>Incl: Observation of Leishman bodies (amastigotes) in dermal lesions, no previous use of anti-leishmanial drugs; no previously confirmed leishmaniasis (by scar or clinically compatible history); no pregnant or lactating women, no acute or chronic medical condition and no history of allergy. Female Px of childbearing age were included after giving consent for effective contraception during therapy and until three months thereafter.<br>Excl: not explicitly reported, but can be inferred from the above inclusion criteria.<br>*Leishmania* species: *L. major*. |

**Mohebali 2007** (*Continued*)

| | |
|---|---|
| Interventions | T1: Miltefosine orally 2.5 mg/kg daily for 28 days<br>n = 32. Mean number of lesions: 2.7 (1 to 15). Mean ulcer size: 27.1 (0.9 to 80.0) $mm^2$. Mean lesion duration: 45.4 days.<br>T2: IMMA at 20 mg/kg/d for 14 days<br>n = 31. Mean number of lesions: 2.5 (1 to 10). Mean ulcer size: 19.3 (3-67.3) $mm^2$. Mean lesion duration: 43.6 days.<br>Miltefosine capsules were administered as follows:<br>9 to 14 Kg 3 Cap. 10 mg; 15 to 29 Kg 1 Cap. 50 mg: 30 to 45Kg 2 Cap. 50 mg; 46 to 84 Kg 3 Cap. 50 mg |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' three months after treatment<br>*Secondary outcomes*<br>Duration of remission and percentage of people with treated lesions that recur within six months<br>Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | Balanced block method |
| Blinding?<br>All outcomes | No | open label |
| Intention-to-treat/Drop-outs? | Yes | 5 out of 63 (< 10%) |

**Momeni 1996**

| | |
|---|---|
| Methods | FU: 51 days<br>D: Randomised clinical trial |
| Participants | Iran<br>n =1 40 (131 completed the study)<br>M/F: 90/41. The mean age was 26.3 years, the youngest was 12 years and the oldest 46 years.<br>Incl: age > 12 years, a diagnosis of CL confirmed by laboratory test results, no previous treatment for leishmaniasis, no serious concomitant medical problems.<br>Excl: pregnant and nursing women and Px who had lesions on the face or lesions lasting more than four months. Age < 12 years.<br>*Leishmania* species: *L. major* |

**Momeni 1996** (*Continued*)

| | |
|---|---|
| Interventions | T1: Itraconazole orally 7 mg/kg/d for 3 weeks (max. 400 mg per day)<br>n = 70. Total number of lesions: 219. Mean duration of the disease before treatment: 38 days (1.45 months).<br>T2: Placebo capsules for three weeks.<br>n = 70. Total number of lesions: 262. Mean duration of the disease before treatment: 45 days (1.50 months). |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' 51 days after treatment<br>*Secondary outcomes*<br>Adverse effects |
| Notes | Sample size: Medium/C |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | Carried out by the WHO Special Programme for Research and Training in Tropical Diseases group in Geneva, Switzerland (not stated how they did it) |
| Blinding?<br>All outcomes | Yes | Double-blind: Px and clinicians. The manufacturer (Janssen Pharmaceuticals) coded identical capsules |
| Intention-to-treat/Drop-outs? | No | 9 out of 140 (< 10%) |

**Momeni 2002**

| | |
|---|---|
| Methods | FU: 51 days<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 72<br>Px refereed to the Skin Research Centre in Isfahan city. M/F: 56/16 with 216 lesions. Sixty-six completed the treatment, (50 men (75.7%) and 16 women (24.3%). The mean age was 21.9 years for men and 17.6 for women, the youngest Px was 5 year old girl and the oldest was a 48 year old working man.<br>Incl: Age > 5 years; a diagnosis of CL confirmed by laboratory test results; no previous treatment for leishmaniasis; no serious concomitant medical problems; and signed written informed consent.<br>Excl: Pregnant and nursing women, age < 5 years and Pxs who had lesions lasting for > 4 months.<br>*Leishmania* species: *L. major* |

**Momeni 2002** (*Continued*)

| | |
|---|---|
| Interventions | T1: AL 20 mg/kg per day + low-dose MA 30 mg/kg/day for 20 days.<br>ITT n = 36. Total number of lesions: 91. The mean duration of the disease before therapy: 46.7 days.<br>T2: IMMA 60 mg/kg/ day for 20 days.<br>ITT n = 36. Total number of lesions: 105. The mean duration of the disease before therapy: 45 days. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' 51 days after treatment<br>*Secondary outcomes*<br>Adverse effects<br>*Tertiary outcomes*<br>Microbiological or histopathological cure of skin lesions |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | No | open |
| Intention-to-treat/Drop-outs? | No | 6 out of 62 (< 10%) |

**Momeni 2003**

| | |
|---|---|
| Methods | FU: 51 days<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 90 (73 completed the trial)<br>The study population was drawn from endemic areas in the north of Isfahan city. M/F: 45/28 and the mean age was 19.9 years old ( the youngest was 6 and the oldest was a 60 year old man).<br>Incl: age > 5 years, laboratory-confirmed diagnosis of CL, no previous treatment for leishmaniasis, no serious concomitant medical problems.<br>Excl: pregnant and nursing women, lesions on the face or lesions of > 4 months duration.<br>*Leishmania* species: *L. major* and *L. tropica*. |
| Interventions | T1: Ketoconazole cream for 21 days<br>n = 45. Total number of lesions: 59. The mean duration of the disease before treatment: 38 days.<br>T2: Placebo cream for 21 days<br>n = 45. Total number of lesions: 43. The mean duration of the disease before treatment: 42 days.<br>Frequency: TD for 21 days. |

**Momeni 2003** (*Continued*)

| | |
|---|---|
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' 51 days after treatment<br>*Secondary outcomes*<br>Adverse effects |
| Notes | Sample size: Medium/C |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Yes | Double-blind: Px and clinicians. The tubes were coded and were identical in appearance |
| Intention-to-treat/Drop-outs? | No | 17 out of 90 (< 25%) |

**Mujtaba 1999**

| | |
|---|---|
| Methods | FU: two months<br>D: Randomised clinical trial |
| Participants | Pakistan<br>n = 104<br>M/F: 58/38. Baseline comparability: regarding age, sex, number and site of lesions and duration of the disease.<br>Incl: Clinical diagnosis of CL and positive Giemsa-stained smear of parasite.<br>Excl: > 5 lesions and pregnant women.<br>*Leishmania* species not mentioned. |
| Interventions | T1: ILMA injections weekly until complete cure or up to eight weeks.<br>n = 49 with 111 lesions. Number of lesions: 21 Px had single lesions and 28 had 2 lesions or more. Duration of the disease: 36 Px < 6 months and 13 > 6 months.<br>T2: ILMA injections fortnightly until complete cure or up to eight weeks.<br>n = 55 (only 47 in the analyses because 8 were lost to FU) 104 lesions (for the 47). Number of lesions: 19 Px had single lesions and 28 had 2 lesions or more. Duration of the disease: 36 Px < 6 months and 11 > 6 months.<br>Each ampoule of 5 ml containing 425 mg of the salt |
| Outcomes | *Primary outcome*<br>Percentage of lesions 'cured' two months after treatment<br>*Secondary outcomes*<br>Speed of healing (time taken to be 'cured')<br>Duration of remission and percentage of people with treated lesions that recur within six months, one, two and three years: time assessment not specified<br>Prevention of scarring |

**Mujtaba 1999** (*Continued*)

| | |
|---|---|
| | Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Unclear | no mention about blinding |
| Intention-to-treat/Drop-outs? | No | 8 out of 104 (<10%) |

**Nassiri-Kashani 2005**

| | |
|---|---|
| Methods | FU: three months<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 200<br>Duration of < 45 days. Baseline comparability: Comparable with regard to age, sex and duration of the lesions.<br>Incl: age between 12 and 60 years old, presence of parasitologically confirmed lesion(s) of CL, and healthiness on the basis of physical examination, medical history, and the results of blood biochemistry and haematology, carried out < 2 weeks before the start of the trial.<br>Excl: women of child-bearing age without adequate effective contraception, pregnant or breast feeding, duration of lesions > 45 days, the presence of lesions on the face or near the mucous membranes, > 5 lesions or any lesion with a diameter > 3 cm, history of any systemic antileishmanial therapy, known hypersensitivity/allergy to itraconazole, and receiving any drug with known interaction with itraconazole.<br>*Leishmania* species: *L. major*<br>Compliance assessed by asking Px to bring back the unused medication at the next visit. |
| Interventions | T1: Itraconazole 200 mg OD for 8 weeks<br>n = 100. Mean number of lesions: 2.5, ulcer size: 7.76 mm.<br>T2: Placebo for eight weeks<br>n = 100. Mean number of lesions: 2.2, ulcer size: 8.58 mm. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' three months after treatment<br>*Secondary outcomes*<br>Adverse effects |
| Notes | Sample size: Large/C |

**Nassiri-Kashani 2005** (*Continued*)

| ***Risk of bias*** | | |
|---|---|---|
| **Item** | **Authors' judgement** | **Description** |
| Adequate sequence generation? | Yes | Random number table |
| Allocation concealment? | Yes | Concealed from the investigator until the data entry was completed and the data bank was locked |
| Blinding?<br>All outcomes | Yes | Double-blind: Px and outcome assessors |
| Intention-to-treat/Drop-outs? | No | 42 out of 200 (< 25%) |

**Nilforoushzadeh 2004**

| | |
|---|---|
| Methods | FU: six weeks<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 210 (157 completed the study)<br>Baseline comparability: comparable regarding sex, age, and clinical type of lesions (claimed but data were not presented).<br>Incl: CL confirmed with direct smear, age 1 to 20 years, maximum number of lesions 3, maximum size of lesion 5 cm, duration of disease less than 8 weeks.<br>Excl: history of allergy to MA, pregnancy or lactating.<br>*Leishmania* species: not mentioned. |
| Interventions | T1: ILMA twice every week till complete healing or for a maximum of six weeks<br>(n = 81)<br>T2: Combination triple therapy consisting of: 1- 15% PR+10% urea applied TD for 4 weeks: 2- cryotherapy with liquid nitrogen repeated every two weeks till complete healing or for a maximum of three sessions, 3- ILMA similar to group one (in sessions that both cryotherapy and injections were used, cryo was done before injections)<br>(n = 76) |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' two weeks after treatment |
| Notes | Sample size: Large/NC |

| ***Risk of bias*** | | |
|---|---|---|
| **Item** | **Authors' judgement** | **Description** |

**Nilforoushzadeh 2004** (*Continued*)

| | | |
|---|---|---|
| Blinding?<br>All outcomes | No | |
| Intention-to-treat/Drop-outs? | No | 53 out of 210 (< 55%) |

**Nilforoushzadeh 2006**

| | |
|---|---|
| Methods | FU: three months<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 80<br>A total number of 80 Px (5 to 75 years) referred to Skin Disease and Leishmaniasis Research Center (SDLRC), Isfahan, Iran. The most common clinical type of the lesions in both groups was papule (50% in TCA and 44% in the MA group) and nodule (25% in TCA and 24% in the MA group).<br>Incl: CL confirmed with direct smear.<br>Excl: If they were pregnant or nursing mothers, were treated previously for CL, had any known intercurrent illness or a history of allergy to MA, palpebral lesions, having > 5 lesions or a lesion > 3 cm, or if the duration of lesions was > 12 weeks.<br>*Leishmania* species: not mentioned |
| Interventions | T1: Trichloroacetic acid (TCA) 50% (wt/vol) was applied on the lesions applied every two weeks up to three times<br>n = 40. Mean number of lesions: 1.2.<br>T2: ILMA weekly up to six weeks<br>n = 40. Mean number of lesions: 1.4. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' at the end of treatment<br>*Secondary outcomes*<br>Duration of remission and percentage of people with treated lesions that recur after three months FU<br>Adverse effects<br>*Tertiary outcomes*<br>Microbiological or histopathological cure of skin lesions |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Adequate sequence generation? | Yes | Random digit table |

**Nilforoushzadeh 2006** (*Continued*)

| | | |
|---|---|---|
| Blinding?<br>All outcomes | No | open |
| Intention-to-treat/Drop-outs? | No | 7 out of 80 (< 10%) |

**Nilforoushzadeh 2007**

| | |
|---|---|
| Methods | FU: fourmonths<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 100<br>A total number of 100 Px (7 to 70 years) referred to Skin Disease and Leishmaniasis Research Center (SDLRC), Isfahan, Iran. The most common clinical type of the lesions in both groups was plaque (60% in Honey + MA and 55.6% in the MA group).<br>Incl: CL confirmed with direct smear, no history of systemic or topical therapy for CL, absence of the malnutrition or severe predisposing disease such as cardiac, renal or hepatic disease and other contraindication for MA.<br>Excl: If they were pregnant or lactating mothers, lesions > 3 months old and treated with the drugs that had interaction with MA.<br>*Leishmania* species: not mentioned |
| Interventions | T1: Topical honey soaked gauze TD plus ILMA<br>n = 50. Mean number of lesions: 1.3.<br>T2: ILMA<br>n = 50. Mean number of lesions: 1.7.<br>Frequency: once weekly until complete healing of the ulcer or for maximum of six weeks. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' 2.5 to 3 months after treatment<br>*Secondary outcomes*<br>Speed of healing (time taken to be 'cured') |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Adequate sequence generation? | Yes | Random allocation software (ver 1.0, May 2004; Saghaei) |
| Blinding?<br>All outcomes | No | open |
| Intention-to-treat/Drop-outs? | No | 23 out of 100 (< 25%) |

**Reithinger 2005**

| | |
|---|---|
| Methods | FU: 100 days after initiation of treatment<br>D: Randomised clinical trial |
| Participants | Afghanistan<br>n = 431 (259 completed the trial)<br>Kabul residents. Parasite identification was by PCR at Leeds University (UK). Study carried out at the Health net International khair khana clinic. Age range 10 to 20, M/F: 200/201. The lesions were primarily located on the face (43.4% of Px), on the hands (38.2%), legs (15.9%) and arms (2.4%).<br>Incl: age of > 5 years, the presence of a single, parasitologically confirmed CL lesion, and no prior history of disease and/or antimonial treatment.<br>Excl: the presence of a CL lesion located on or immediately adjacent to the nose, lips, or eyes, pregnancy, breast-feeding, major surgery in the previous three months, presence of any uncontrolled medical condition, and anticipated unavailability for FU.<br>*Leishmania* species: *L. tropica*. PCR-positive for *Leishmania* DNA: 69% (27/39); *L. tropica* identified: for all 27. |
| Interventions | T1: IL SSG a total of 5 injections of 2 to 5 ml every 5 to 7 days depending on the lesion size for a total of up to 29 days.<br>n = 93/148. MNL: 1. MSL: 12.75 mm. MDLBT: 6 months.<br>T2: IM SSG (20 mg/kg) daily for 21 days.<br>n = 58/144. MNL: 1. MSL: 13.75 mm. MDLBT: 5.5 months.<br>T3: Thermotherapy using radio-frequency waves (1 treatment of > 1 consecutive application at 50$^{o}$C for 30 s depending on lesion size).<br>n = 108/139. MNL: 1. MSL: 10.25 mm. MDLBT: 6 months.<br>Co-treatment: if systemic treatment was required, Px received treatment with an antibiotic that has no activity against *Leishmania* (e.g., erythromycin). |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' two months after treatment<br>*Secondary outcomes*<br>Speed of healing (time taken to be 'cured')<br>Quality of life<br>Adverse effects |
| Notes | Sample size: Large/C |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | Px proceeded to pick one of three identical cardboard pieces out of a hat (the cardboard had been labelled with different treatment codes on one of its sides). After Px were randomly assigned to receive a treatment, the cardboard piece picked was returned to the hat |

**Reithinger 2005** (*Continued*)

| | | |
|---|---|---|
| Blinding?<br>All outcomes | No | |
| Intention-to-treat/Drop-outs? | Yes | 172 out of 431 (< 55%) |

**Sadeghian 2006**

| | |
|---|---|
| Methods | FU: three months<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 64 (63 completed the study)<br>Duration of the disease approximately 1.3 months. M/F: 29/34. Px from pentoxifylline + MA were approx 27 years of age, 59.5% had plaque, 24.5% nodule and 16% papule type of lesions and they were primarily located in the face (35%), upper limbs (24.5%), lower limbs (21%) and trunk (19.5%). Px from the MA + placebo were approx 31 years of age, 42.7% had plaque, 33.6% nodule and 23.7% papule type of lesions and they were primarily located in the face (33.5%), upper limbs (24.3%), lower limbs (22%) and trunk (20.2%).<br>Incl: CL in whom the diagnosis was confirmed by laboratory demonstration of the parasite in the lesions by direct smear.<br>Excl: allergic to antimonial drugs or pentoxifylline, lacting and pregnant and who had history of systemic illness.<br>*Leishmania* species: *L. major* |
| Interventions | T1: pentoxifylline orally (400 mg 3 times daily)<br>n = 32 with 143 lesions. MNL: 4. MDLBT: 1.2 months.<br>T2: placebo<br>n = 31 with 164 lesions. MNL: 5. MDLBT: 1.3 months.<br>Frequency: 3 times daily for 20 days.<br>Co-treatment: IMMA (20 mg/kg/day) |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' threemonths after treatment<br>*Secondary outcomes*<br>Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Blinding?<br>All outcomes | Yes | Double-blinded: Px and clinicians |

**Sadeghian 2006** (*Continued*)

| | | |
|---|---|---|
| Intention-to-treat/Drop-outs? | No | 1 out of 64 (< 10%) |

**Sadeghian 2006B**

| | |
|---|---|
| Methods | FU: six months<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 72<br>The trial was conducted in the Skin Diseases and Leishmaniasis Research Center in Isfahan. In the MA group, the mean age was 18.67 years and in the hypertonic sodium chloride group (HSCS) was 20.52 years. The most common site of lesions was on the extremities and the least common site was the trunk in both groups. Baseline comparability: regarding age, size of lesions, duration of the disease. However, no tables are shown but they put the figures and the statistical values in the text.<br>Incl: Px with positive smear for Leishman bodies, of both sexes and > 5 years old who did not have indication for systemic therapy.<br>Excl: Px with facial lesions or lesions on joints, sporotrichoid type, lupoid leishmaniasis, erysipeloid type and other atypical forms of CL, pregnant women and Px with history of cardiovascular and renal diseases.<br>*Leishmania* species: *L. major* endemic in the area. |
| Interventions | T1: IL HSCL (NaCl 5%; 0.5 to 1 ml)<br>n = 36. The size range of lesions were from 0.5 to 4 $cm^2$.<br>T2: ILMA (0.5 to 1 ml)<br>n = 36. The size range of lesions were from 0.5 to 4 $cm^2$.<br>Frequency: weekly six to ten weeks. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' at the end of treatment<br>*Secondary outcomes*<br>Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Blinding?<br>All outcomes | Unclear | no mention about blinding |
| Intention-to-treat/Drop-outs? | Yes | ND |

**Sadeghian 2007**

| | |
|---|---|
| Methods | FU: six months<br>D: Randomised clinical trial |
| Participants | Iran<br>n =117<br>Skin Diseases and Leishmaniasis Research Center. In total, 57 Px M/F: 37/20 with 83 lesions and 25.12 years of age were enrolled in the group treated with controlled localized heating using an RF heat generator, and 60 Px (M/F: 29/31) with 94 lesions and 22.6 years of age in the group treated ILMA. Lesions were located in the trunk and upper and lower limbs. The shape of lesions were papule, nodule and plaque-like.<br>Incl: if the examination of a smear from a suspected CL lesion was confirmed positive for *Leishmania*.<br>Excl: Pregnant women, children < 5 years of age, Px with facial lesions, those who had already received or were under other specific antileishmanial therapy, and Px with significant underlying diseases.<br>*Leishmania* species: not reported. |
| Interventions | T1: Controlled localized heating using an RF heat generator (4 MHz, maximum output 90 W). The affected area was heated to 50ºC surface temperature for 30 s<br>n = 57. Mean number of lesions: 1.4. Mean duration of the disease: 4.42 weeks. Mean largest diameter: 15.6 mm.<br>T2: ILMA. The volume of the drug was 0.1 to 4 ml (each ml contains 85 mg MA), depending on lesion size<br>n = 60. Mean number of lesions: 1.5. Mean duration of the disease: 3.85 weeks. Mean largest diameter: 14.7 mm.<br>Frequency: once weekly for four consecutive weeks. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' six months after treatment<br>*Secondary outcomes*<br>Duration of remission and percentage of people with treated lesions that recur within six months<br>Prevention of scarring<br>Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | Random number list generated by Epi Info |
| Blinding?<br>All outcomes | Yes | Single-blind: outcome assessor |
| Intention-to-treat/Drop-outs? | Yes | ND |

**Salmanpour 2001**

| | |
|---|---|
| Methods | FU: 24 weeks<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 96<br>M/F: 44/52, with an age range of 3 to 64 years old.<br>Incl: Px with CL confirmed parasitologically by direct skin smears or skin biopsies.<br>Excl: Children < 3 years of age, pregnant and lactating women, and cases with concomitant renal, liver or heart disease, and any event of any laboratory abnormality prior to initiation of treatment.<br>*Leishmania* species: *L. tropica* and *L. major*. |
| Interventions | T1: Ketoconazole (Adults: 600 mg/day for 30 days and children: 10 mg/kg/day for 30 days)<br>n = 64. MNL: 2.5. MDLBT: 2.6 months.<br>T2: ILMA six injections (some received up to eight)<br>n = 32. MNL: 2.3. MDLBT: 3.1 months.<br>There is no mention about frequency of injections in MA group. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' at 1.5 months (6 weeks) after treatment<br>*Secondary outcomes*<br>Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Unclear | no mention about blinding |
| Intention-to-treat/Drop-outs? | Yes | ND |

**Salmanpour 2006**

| | |
|---|---|
| Methods | FU: not reported<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 60<br>The Dermatology Clinic of Faghihi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran. Lesions were located on the head, neck and lower and upper extremities. Lesion duration was divided in two groups: a duration of < 3 months and > 3 months. Regarding lesion size, the authors divided the sizes in three groups: < 1cm, between 1 and 3 cm and >3 cm. Baseline comparability: not reported.<br>Incl: Px with CL confirmed. |

**Salmanpour 2006** (*Continued*)

| | |
|---|---|
| | *Leishmania* species: not reported. |
| Interventions | T1: Cryotherapy. The freezing time was 10 to 30 s with a thawing interval of 20 s,<br>n = 20.<br>T2: Combination of cryotherapy and ILMA. The participants first received cryotherapy and, after 5 to 10 min, were given ILMA<br>n = 20.<br>T3: ILMA. The solution was injected into each lesion (0.2 to 1.5 $cm^3$ per session per week, depending on the size)<br>n = 20.<br>Frequency: weekly for a total of six to eight times for each case. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' : timing not reported.<br>*Secondary outcomes*<br>Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Unclear | no mention about blinding |
| Intention-to-treat/Drop-outs? | Yes | ND |

**Sharquie 1997**

| | |
|---|---|
| Methods | FU: six weeks<br>D: Randomised clinical trial |
| Participants | Iraq<br>n =85 (63 completed the study)<br>M/F: 28/37. Age range from 3 months to 65 years old. Px came from different parts of the city of Baghdad, from parts of the Governorate of Baghdad or other areas surrounding Baghdad.<br>Px with typical lesions of acute CL, they had single or few skin lesions. Of the 85 Px, 63 were followed-up, Px who did not show up after the first or second injection were excluded. Px were not randomly selected for the control group.<br>Incl: Confirmed cases of CL by smear or culture, or both. Acute CL with a history of 12 weeks or less. This criterion was applied to exclude any possibility of self healing of lesions during the period of FU.<br>Excl: Cases of reinfection.<br>*Leishmania* species: *L. major* and *L. tropica* endemic in the area. |

**Sharquie 1997** (*Continued*)

| | |
|---|---|
| Interventions | T1: IL ZS with a solution of 2%<br>n = 19. MNL: 2.0. MDLBT: 6.89 weeks.<br>T2: IL Hypertonic 7% sodium chloride<br>n = 17. MNL: 2.35. MDLBT: 7.65 weeks.<br>T3: IL SSG 100 mg/ml<br>n = 18. MNL: 1.94. MDLBT: 7.00 weeks.<br>T4: Control: A few lesions on unimportant and unexposed parts of the body were left as controls.<br>n = 9. MNL: 4.22. MDLBT: 8.89 weeks.<br>In the cases where there was slight to mild improvement, another injection was given. We are not aware of the time left between each injection |
| Outcomes | *Primary outcome*<br>Percentage of lesions 'cured' 1.5 months (6 weeks) after treatment<br>*Secondary outcomes*<br>Speed of healing (time taken to be 'cured')<br>Prevention of scarring<br>Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Unclear | no mention about blinding |
| Intention-to-treat/Drop-outs? | No | 22 out of 85 (< 55%) |

**Sharquie 2001**

| | |
|---|---|
| Methods | FU: 45 days<br>D: Randomised clinical trial |
| Participants | Iraq (out-patient department)<br>n = 130 (104 completed the study)<br>M/F: 62/68 coming from different parts of the city of Baghdad, for other parts of the Governorate of Baghdad, and from surrounding Governorates.<br>Incl: CL confirmed by smear/culture. Acute CL of 12 weeks or less duration, (to exclude the possibility of self healing). Selected Px were those for whom systemic treatment was indicated including those for whom having multiple lesions ( > 5) or large lesions ( > 4 $cm^2$), that could not be injected, or who had lesions near to critical areas such as the eye; very young children for whom no local injection was attempted; and Px who refused local treatment (2%).<br>Excl: Any Px who received antileishmanial treatment, either local or systemic, and cases of reinfection.<br>*Leishmania* species: *L. major* and *L. tropica* cause CL in Iraq. |

**Sharquie 2001** (*Continued*)

| | |
|---|---|
| Interventions | T1: ZS orally 2.5 mg/kg,<br>n = 31 (ITT 39). MNL: 5.19. MDLBT: 8.1 weeks.<br>T2: ZS orally 5 mg/kg<br>n = 29 (ITT 37). MNL: 5.00. MDLBT: 7.95 weeks.<br>T3: ZS orally 10 mg/kg<br>n = 32 (ITT 39). MNL: 4.65. MDLBT: 8.5 weeks.<br>T4: Control<br>n = 12 (ITT 15). MNL: 3.50. MDLBT: 8.89 weeks.<br>Frequency: ZS groups one capsule every eight h |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' 1 month (day 45) after treatment<br>*Secondary outcomes*<br>Speed of healing (time taken to be 'cured')<br>Prevention of scarring<br>Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | No | open (both Px and doctor were aware that the Px was receiving treatment, but they were unaware of the dose) |
| Intention-to-treat/Drop-outs? | No | 26 out of 130 (< 25%) |

**Shazad 2005**

| | |
|---|---|
| Methods | FU: one and six weeks for clinical evaluations. Px were visited once at six months after treatment was completed<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 60<br>Performed in a Military Base Clinic. All men. Px from the PR group were approx 20.6 years of age, 76.7% had ulcerative, 8.3% nodular and 15% papular type of lesions and they were primarily located in the head and neck (25%), upper extremities (41.7%), lower extremities (31.7%) and trunk (1.7%). Px from the MA group were approx 21.7 years of age, 69.7% had ulcerative, 11.8% nodule and 18.4% papule type of lesions and they were primarily located in the head and neck (13.2%), upper extremities (47.4%), lower extremities (36.8%) and trunk (2.6%).<br>Incl: proven cases of CL, healthy apart from CL, lesions not in close proximity to a vital organ or joint, number of lesions 1 to 3, ulcer size < 5 cm in diameter, onset of the lesions < 3 months, no previous standard anti-*Leishmania* treatment, and no history of allergy to the paromomycin family. |

**Shazad 2005** (*Continued*)

| | |
|---|---|
| | Excl: not reported.<br>*Leishmania* species: *L. major*<br>Compliance assessment: the ointments were used under the observation of medical staff. |
| Interventions | T1:15% PR sulfate and 10% urea. Dose: 0.5 mg/mm$^2$/day TD for 20 days.<br>n = 29/30 and 60 lesions. MNL: 2. MSL 21.7 mm. MDLBT: 37.8 days.<br>T2: intradermal MA every other day for 20 days.<br>n = 27/30 and 76 lesions. MNL: 2.4. MSL: 25 mm. MDLBT: 39 days. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' one week after treatment<br>*Secondary outcomes*<br>Adverse effects |
| Notes | Sample size: Medium/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | Unclear | no mention about blinding |
| Intention-to-treat/Drop-outs? | No | 4 out of 60 (< 10%) |

**Zerehsaz 1999**

| | |
|---|---|
| Methods | FU: six weeks<br>D: Randomised clinical trial |
| Participants | Iran<br>n = 171<br>Px mostly from the city of Shiraz, with a few from other smaller cities in Fars province. M/F: 84/87 with an age range from 10 months to 69 years. The duration of the disease was < 4 months. The majority of Px had papular and papulonodular lesion(s), although other clinical forms including ulcerative, eczematoid, hyperkeratotic, and erysipeloid types were also present. The majority of Px had multiple lesions and the most common sites were the face and the extremities.<br>Incl: Diagnosed as having CL based on positive smears from lesions, and in some cases, cultures and histopathologic studies were also performed.<br>Excl: if they were pregnant or nursing or if they had serious concomitant diseases.<br>*Leishmania* species: *L. major* and *L. tropica* in the area. |

**Zerehsaz 1999** (*Continued*)

| | |
|---|---|
| Interventions | T1: Herbal extract Z-HE as a black past applied to the lesions and covered by a dressing for 5 consecutive days + placebo (saline) injected (0.5 ml) for 20 consecutive days<br>n = 86<br>T2: IMMA (15 to 20 mg/kg/d) for 20 consecutive days + placebo (petrolatum and charcoal powder) applied on the lesions as a black paste covered by a dressing for 5 consecutive days.<br>n = 85 |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' 1.5 months (6 weeks) after treatment<br>*Secondary outcomes*<br>Adverse effects |
| Notes | Sample size: Large/NC |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Blinding?<br>All outcomes | Yes | Double-blind: only stated but not reported who was blinded |
| Intention-to-treat/Drop-outs? | Yes | ND |

**Özgöztasi 1997**

| | |
|---|---|
| Methods | FU: four weeks<br>D: Randomised clinical trial |
| Participants | Turkey<br>n = 72<br>The majority were children aged ten years or younger. The most common site of the lesion was the face and most of the Px had one lesion, with duration of the lesions varying from 1 to 12 months, had papulonodular lesions.<br>Incl: confirmed diagnosis of CL.<br>Excl: if pregnant or nursing or if they had serious concomitant diseases.<br>*Leishmania* species: *L. tropica* in the area. |
| Interventions | T1: 15% PR sulphate + 12% MBCL TD for 15 days.<br>n = 40. MNL: 1. MDLBT: 4.3 months.<br>T2: Ketoconazole orally 400 mg per day for 30 days (reduced to 200 mg if Px < 12 years old)<br>n = 32. MNL: 1. MDLBT: 4.3 months. |
| Outcomes | *Primary outcome*<br>Percentage of Px 'cured' one month after treatment<br>*Secondary outcomes*<br>Adverse effects |

**Özgöztasi 1997** (*Continued*)

| | |
|---|---|
| Notes | Sample size: Medium/NC |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Blinding?<br>All outcomes | No | open |
| Intention-to-treat/Drop-outs? | Yes | ND |

FU: follow-up; D: design; Px: participants; M/F: men/women ratio; Incl: inclusion crtieria; Excl: exclusion criteria; m/f: male/female; T1: treatment 1; T2: treatment 2; T: treatment 3; T4: treatment 4; IM: intramuscular; IL: intralesional; IV: intravenous; OD: once daily; TD: twice daily; MA: meglumine antimoniate; SSG: sodium stibogluconate; AL: allopurinol; PDT: Topical Photodynamic therapy; PR: paromomycin; MBCL: methylbenzethonium chloride; ZS: Zinc sulphate; MNL: Median number of lesions; MSL: Median size of lesions; MDLBT: Median duration of lesions before therapy; Drop-outs: ND = no drop-outs; < 10% = less than 10%; < 25% = greater than 10% but less than 25%; < 55%= greater than 25% but less than 55%; Sample size: Small = < 50 participants; Medium = 51 to 150 participants; Large = > 150 participants; C: calculated; NC: not calculated

## Characteristics of excluded studies *[ordered by study ID]*

| | |
|---|---|
| Dogra 1986 | They stated that participants were randomly selected for the study, but not randomly assigned to the treatment groups |
| Dogra 1994 | They stated that participants were randomly selected for the study, but not randomly assigned to the treatment groups |
| El On 1992 | Cross-over study |
| Frankenburg 1993 | It measured immunity parameters but did not show any clinical results. |
| Moosavi 2005 | The method of generation of randomisation was inappropriate. The author was contacted and stated that after enrolling the participants, they did consecutively intralesional meglumine antimoniate for odd number participants and used topical paromomycin for even number participants. |
| Singh 1995 | They stated that participants in both groups were randomly selected. However, they did not have an initial population eligible for the study that was randomly divided in the two treatment groups. But rather one group of people that were randomly selected for one group and another group of participants that were also randomly selected to form part of the other group. Besides, the duration of treatments were not the same and the follow-up was also different for both treatment groups. |

(*Continued*)

| | |
|---|---|
| Trau 1987 | No clear data is available for multiple lesions. Only lesions from participants with multiple lesions were randomised. The lesions from participants with single lesions a cross-over study was performed. |

## Characteristics of studies awaiting assessment *[ordered by study ID]*

**Layegh 2007**

| | |
|---|---|
| Methods | Followed up: 16 weeks.<br>Losses to follow-up: In the azithromycin group, 2 Px withdrew because of GI symptoms (no ITT analysis were performed in this study). |
| Participants | 49 Px from Iran |
| Interventions | 22 received 500 mg/day azithromycin for 5 days/month. Treatment cycles were repeated monthly to a maximum of 4 months; 27 Px received 60 mg/kg IMMA for 20 days. |
| Outcomes | The response rates of 20 Px (29 lesions) were as follows: full improvement, 10.3%; partial improvement, 27.6%; and 62.1%, no response. In the IMMA group with 27 Px (58 lesions), these rates were 34.4%, 13.8%, and 51.7%, respectively |
| Notes | |

Px: Participants; IM: intramuscular; MA: meglumine antimoniate.

## Characteristics of ongoing studies *[ordered by study ID]*

- All of the participants had positive smear for leishmanin body and have not received any topical or systemic therapy for leishmaniasis.
- The age of participants was between 7 to 70 years old.

Exclusion criteria:

- participants who were pregnant or lactating
- participants with history of cardiac, renal, hepatic diseases
- participants with any contraindication for treatment

**ISRCTN32701387**

| | |
|---|---|
| Trial name or title | A comparative study of the efficacy of combination therapy with oral omeprazole and low dose of systemic meglumine antimoniate versus the standard dose of systemic meglumine antimoniate in the treatment of cutaneous leishmaniasis |
| Methods | |
| Participants | Double-blind, randomised study<br>Iran<br>Inclusion criteria:<br>• All of the participants had positive smear for leishmanin body and have not received any topical or systemic therapy for leishmaniasis.<br>• The age of participants was between 7 to 70 years old.<br>Exclusion criteria:<br>• participants who were pregnant or lactating<br>• participants with history of cardiac, renal, hepatic diseases<br>• participants with any contraindication for treatment |
| Interventions | IM 60 mg/kg/day MA and placebo for three weeks.<br>IM 30 mg/kg/day MA and 40 mg of the oral omeprazole for three weeks.<br>IM 30 mg/kg/day MA and oral placebo for three weeks |
| Outcomes | *Primary outcome measure(s)*<br>Healing rate during the course of treatment was more in the groups treated with standard dose glucantime and placebo and low dose glucantime and omeprazole than the group treated with low dose glucantime and placebo (P <0.05).<br>*Secondary outcome measure(s)*<br>Combination therapy with oral omeprazole and low dose of glucantime can be used as alternative treatment for leishmaniasis especially in participants with history of cardiac, renal, and hepatic disease.<br>participants with cardiac diseases were excluded because of some cardiac effects of the glucantime. However, glucantime is not absolutely contraindicated in participants with cardiac diseases and it can be prescribed with ECG monitoring. The study showed that the use of omeprazole as adjuvant therapy will decrease the dose of glucantime for the treatment of cutaneous leishmaniasis and therefore possibly decrease the risk of cardiac events attributed to the use of full dose of glucantime. |
| Starting date | Study start: June 2004 |
| Contact information | Contact name Dr Mohammad Ali Nilfroushzadeh<br>Contact details Khoram Street<br>Skin Diseases and Leishmaniasis Research Center<br>Isfahan<br>Iran<br>81876-98191<br>Contact telephone +98 (0)31 13373736 |

**ISRCTN32701387** (*Continued*)

| | |
|---|---|
| | Contact email nilfroushzadeh@mui.ac.ir |
| Notes | |

- Men and women between 18 and 50 years old.
- Cutaneous ulcers, nodules, plaques, of more than two weeks of evolution requiring systemic therapy.
- Positive parasitological diagnosis for cutaneous leishmaniasis.
- participants that voluntarily accept to participate in the study and sign the informed consent.
- Disposition to be admitted to hospital, if necessary, and to attend all the visits punctually (initial, treatment and follow up).
- Acceptation of not using any other treatment for cutaneous leishmaniasis while in the study.

Exclusion Criteria:

- Pregnant women.
- Presence of any condition or disease that compromises the patient immunologically (i.e. diabetes, cancer, etc.) or, any other, that, based on the judgment of the researcher, could alter the course of cutaneous leishmaniasis.
- Diffuse cutaneous leishmaniasis.
- Visceral leishmaniasis.
- Complete or incomplete treatment with antimony compounds in the last three months.
- participants with history of hepatic, renal, or cardiovascular disease.
- Mentally or neurologically disabled participants that are considered not fit to approve their participation in the study.

**NCT00480883**

| | |
|---|---|
| Trial name or title | Treatment of Cutaneous Leishmaniasis With Meglumine Antimoniate 20 mg/Kg/Day Versus Meglumine Antimoniate 10 mg/Kg/Day And Tablet Allopurinol 20 mg/Kg/Day |
| Methods | |
| Participants | Study Design: Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study<br>Total enrollment: 620<br>Ages Eligible for Study: 18 Years to 50 Years, Genders Eligible for Study:<br>Inclusion Criteria:<br>• Men and women between 18 and 50 years old.<br>• Cutaneous ulcers, nodules, plaques, of more than two weeks of evolution requiring systemic therapy.<br>• Positive parasitological diagnosis for cutaneous leishmaniasis.<br>• participants that voluntarily accept to participate in the study and sign the informed consent.<br>• Disposition to be admitted to hospital, if necessary, and to attend all the visits punctually (initial, treatment and follow up).<br>• Acceptation of not using any other treatment for cutaneous leishmaniasis while in the study.<br>Exclusion Criteria:<br>• Pregnant women.<br>• Presence of any condition or disease that compromises the patient immunologically (i.e. diabetes, cancer, etc.) or, any other, that, based on the judgment of the researcher, could alter the course of cutaneous leishmaniasis. |

**NCT00480883** (*Continued*)

| | |
|---|---|
| | • Diffuse cutaneous leishmaniasis.<br>• Visceral leishmaniasis.<br>• Complete or incomplete treatment with antimony compounds in the last three months.<br>• participants with history of hepatic, renal, or cardiovascular disease.<br>• Mentally or neurologically disabled participants that are considered not fit to approve their participation in the study. |
| Interventions | MA (20 mg/kg/day/IM, till clinical resolution or a maximum of 28 days)<br>A combination of MA (10 mg/kg/day IM) and AL (20 mg/kg/day/oral) untill clinical resolution or a maximum of 28 days |
| Outcomes | Efficacy and adverse effects |
| Starting date | Study start: May 2007 |
| Contact information | AMER EJAZ, FCPS 00 92 300 928 7063 amer˙ejaz@yahoo.com<br>Pakistan, PUNJAB<br>Combined Military Hospital, KHARIAN CANTONMENT, PUNJAB, 74400, Pakistan; Recruiting<br>AMER EJAZ 00 92 300 928 7063 amer˙ejaz@yahoo.com |
| Notes | Source of monetary suport: combined military hospital |

- Presence of cutaneous leishmaniasis diagnosed by culture or staining techniques on lesion aspirates or smear from scraping on the index lesion
- Five or fewer cutaneous lesions
- Each lesion between 1 and 5 cm in greatest diameter
- Volunteer willing to forego other forms of treatment for CL

Exclusion Criteria:

- Received previous treatment for CL within the last 6 months
- Have difficulty complying with instructions
- Have only one lesion that is not primarily ulcerative or in an area that is difficult to treat - Have a lesion that involves the mucosa
- Have signs or symptoms of disseminated disease
- Be a female with a positive pregnancy test - have active malignancy or history of malignancy except squamous cell carcinoma of the skin that has been removed
- Significant organ abnormality or chronic disease that in the opinion of the investigator would warrant exclusion of the participant from the study or prevent the participant from completing the study
- Receiving any medication with pentavalent antimony or any other therapy for cutaneous leishmaniasis except for mercurichrome
- Participant or parent/guardian unable to understand verbal and/or written Arabic, English or French in which a certified translation of the informed consent is available
- Any immuno-compromising condition including recidivant leishmaniasis (during the past two years) or diabetes
- History of known or suspected idiosyncratic reactions or hypersensitivity to aminoglycosides

Age minimum: 5 Years; Age maximum: 65 Years; Gender: Both

**NCT00606580**

| | |
|---|---|
| Trial name or title | A Pivotal, Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate WR 279,396 and Paromomycin Alone to Treat Cutaneous Leishmaniasis (in Tunisia) |
| Methods | |
| Participants | Study design: Treatment, Randomized, Double Blind (Subject, Caregiver, Investigator), Placebo Control, Parallel Assignment, Safety/Efficacy Study<br>Target sample size: 315<br>Inclusion Criteria:<br>• Presence of cutaneous leishmaniasis diagnosed by culture or staining techniques on lesion aspirates or smear from scraping on the index lesion<br>• Five or fewer cutaneous lesions<br>• Each lesion between 1 and 5 cm in greatest diameter<br>• Volunteer willing to forego other forms of treatment for CL<br>Exclusion Criteria:<br>• Received previous treatment for CL within the last 6 months<br>• Have difficulty complying with instructions<br>• Have only one lesion that is not primarily ulcerative or in an area that is difficult to treat - Have a lesion that involves the mucosa<br>• Have signs or symptoms of disseminated disease<br>• Be a female with a positive pregnancy test - have active malignancy or history of malignancy except squamous cell carcinoma of the skin that has been removed<br>• Significant organ abnormality or chronic disease that in the opinion of the investigator would warrant exclusion of the participant from the study or prevent the participant from completing the study<br>• Receiving any medication with pentavalent antimony or any other therapy for cutaneous leishmaniasis except for mercurichrome<br>• Participant or parent/guardian unable to understand verbal and/or written Arabic, English or French in which a certified translation of the informed consent is available<br>• Any immuno-compromising condition including recidivant leishmaniasis (during the past two years) or diabetes<br>• History of known or suspected idiosyncratic reactions or hypersensitivity to aminoglycosides<br>Age minimum: 5 Years; Age maximum: 65 Years; Gender: Both |
| Interventions | WR 279,396 topical cream<br>Paromomycin topical cream<br>Topical cream placebo |
| Outcomes | *Primary outcome*<br>WR 279,396 is superior to placebo in lesion healing<br>*Secondary outcome*<br>Paromomycin topical cream is superior to placebo in lesion healing [Time Frame: 48 days] |

**NCT00606580** (*Continued*)

| | |
|---|---|
| Starting date | Date of first enrolment: January 2008 |
| Contact information | Afif Ben Salah. Institute Pasteur Tunisia<br>Telephone: 216-71-792-429; Email: afif.bensalah@pasteur.rns.tn |
| Notes | Sponsors: U.S. Army Medical Research and Materiel Command and Walter Reed Army Institute of Research (WRAIR) |

## DATA AND ANALYSES

### Comparison 1. ILMA weekly *versus* ILMA fortnightly for up to 8 weeks; FU: 2 months

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

### Comparison 2. IL SSG *versus* IM SSG in *L. tropica*; FU: 2 months

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

### Comparison 3. Itraconazole (200 mg for 6 to 8 weeks) *versus* placebo; FU: 2 to 3 months

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 3 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 in *L. major* infections | 1 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.2 In *L. tropica* infections | 1 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.3 in both species | 1 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 2 Parasitological cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

### Comparison 4. Fluconazole (200mg for 6 weeks) *versus* placebo in *L.major*; FU: 3 months

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Comparison 5. Oral rifampicin 10 mg/kg/d TD for 4 to 6 weeks versus placebo; FU: 3 months**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Comparison 6. IMMA plus oral pentoxifylline *versus* IMMA plus placebo for 20 days in *L. major*; FU: 3 months**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Comparison 7. Oral miltefosine for 28 days *versus* IMMA for 14 days in *L. major*; FU: 3 months**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Comparison 8. Paromomycin (15% + 10% urea twice daily for 14 days) *versus* placebo (twice daily for 14 days) mainly in *L. major*; FU: 2.5 months**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 2 | 383 | Risk Ratio (M-H, Random, 95% CI) | 1.00 [0.86, 1.17] |
| 2 Parasitological cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Comparison 9. Paromomycin (15% + 12% MBCL twice daily x 28 days) *versus* placebo (twice daily for 28 days) in *L. major*; FU: 2 months**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2 Prevention of scarring | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Parasitological cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Comparison 10. Paromomycin (15%+ 12% MBCL twice daily x 28 days) *versus* PDT (weekly for 4 weeks) in *L. major*; FU: 2 months**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2 Prevention of scarring | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Parasitological cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Comparison 11. Paromomycin (4 weeks) *versus* paromomycin (2 weeks) + placebo (2 weeks) in *L. major*; FU: 2.5 months**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2 Parasitological cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Comparison 12. Imiquimod (5% 3 times/week x 28 d) + IMMA (20 mg/kg/d x 14 d) *versus* placebo + i.m. MA in *L.tropica*; FU: 3.5 months**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Comparison 13. PDT (weekly for 4 weeks) *versus* placebo in *L. major*: FU: 2.5 months**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2 Prevention of scarring | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Parasitological cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Comparison 14. Heat *versus* ILMA once a week for 4 weeks: FU: 6 months**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 Lesions | 1 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.2 Participants | 1 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |

**Comparison 15. Thermotherapy *versus* IM and IL SSG in *L. tropica*; FU: 2 months**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 Thermotherapy *versus* IM SSG | 1 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.2 Thermotherapy *versus* IL SSG | 1 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |

**Comparison 16. Topical honey plus ILMA *versus* ILMA ; FU: 2.5 to 3 months**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete cure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

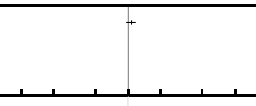
**Analysis 1.1. Comparison 1 ILMA weekly *versus* ILMA fortnightly for up to 8 weeks; FU: 2 months, Outcome 1 Complete cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 1 ILMA weekly ***versus*** ILMA fortnightly for up to 8 weeks; FU: 2 months

Outcome: 1 Complete cure

| Study or subgroup | ILMA weekly n/N | ILMA fortnightly n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Mujtaba 1999 | 102/111 | 89/104 | | 1.07 [ 0.98, 1.18 ] |

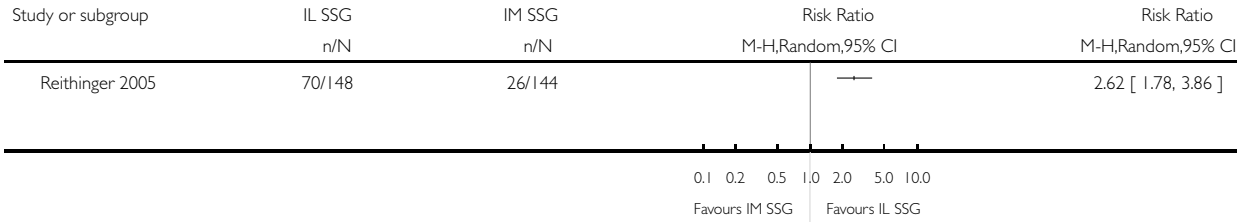


### Analysis 2.1. Comparison 2 IL SSG *versus* IM SSG in *L. tropica*; FU: 2 months, Outcome 1 Complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 2 IL SSG *versus* IM SSG in *L. tropica*; FU: 2 months

Outcome: 1 Complete cure

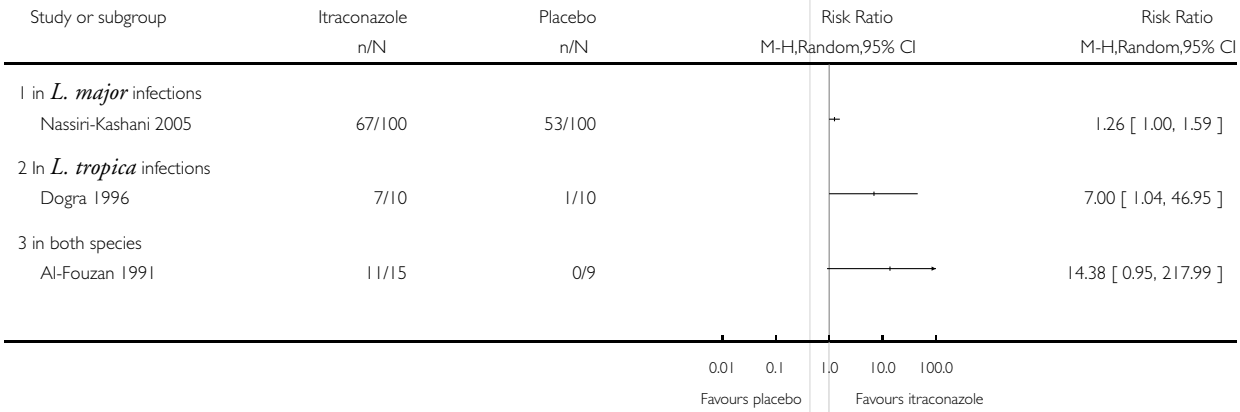



### Analysis 3.1. Comparison 3 Itraconazole (200 mg for 6 to 8 weeks) *versus* placebo; FU: 2 to 3 months, Outcome 1 Complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 3 Itraconazole (200 mg for 6 to 8 weeks) *versus* placebo; FU: 2 to 3 months

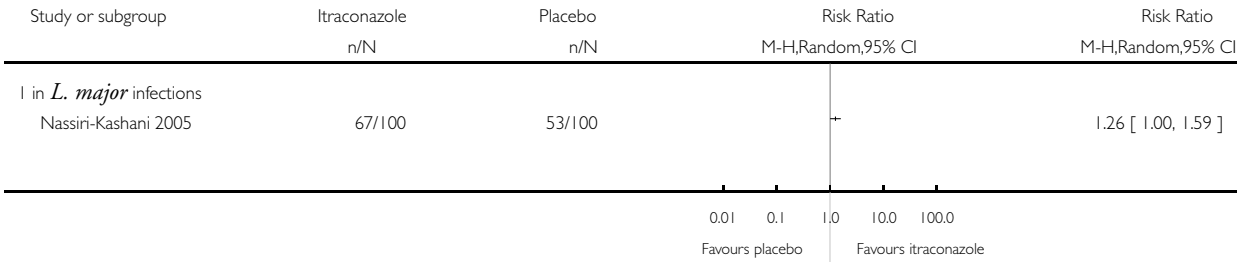
Outcome: 1 Complete cure



Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 3 Itraconazole (200 mg for 6 to 8 weeks) ***versus*** placebo; FU: 2 to 3 months

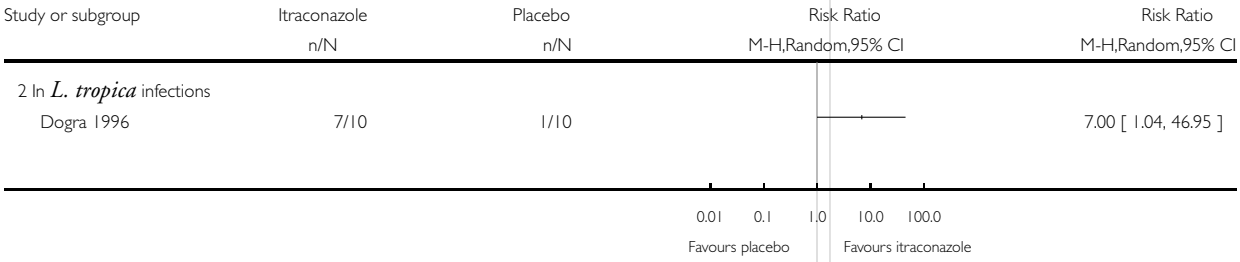
Outcome: 1 Complete cure




Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 3 Itraconazole (200 mg for 6 to 8 weeks) ***versus*** placebo; FU: 2 to 3 months

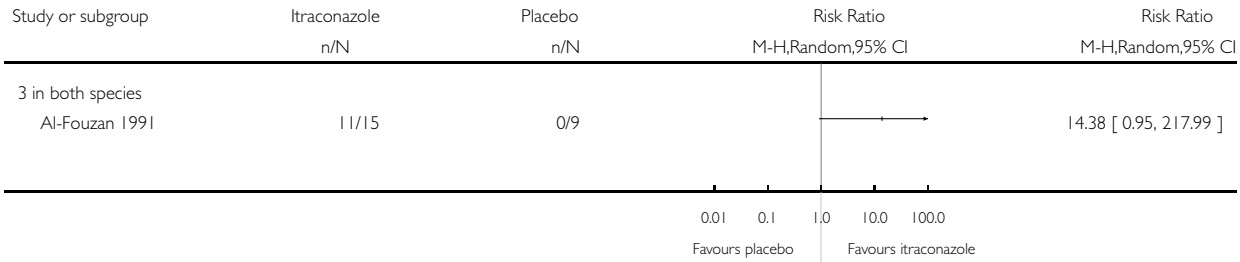
Outcome: 1 Complete cure



Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 3 Itraconazole (200 mg for 6 to 8 weeks) *versus* placebo; FU: 2 to 3 months

Outcome: 1 Complete cure

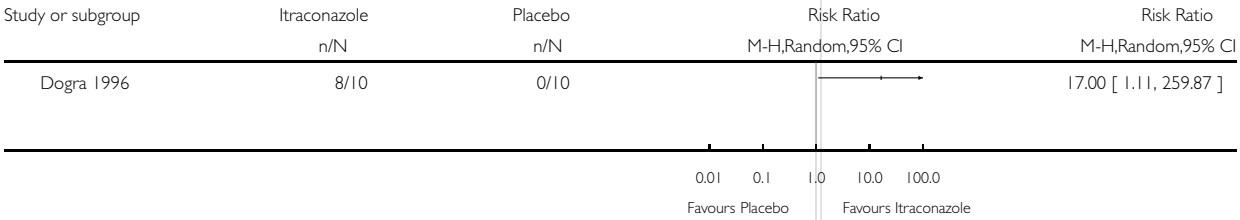



**Analysis 3.2. Comparison 3 Itraconazole (200 mg for 6 to 8 weeks) *versus* placebo; FU: 2 to 3 months, Outcome 2 Parasitological cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 3 Itraconazole (200 mg for 6 to 8 weeks) *versus* placebo; FU: 2 to 3 months

Outcome: 2 Parasitological cure

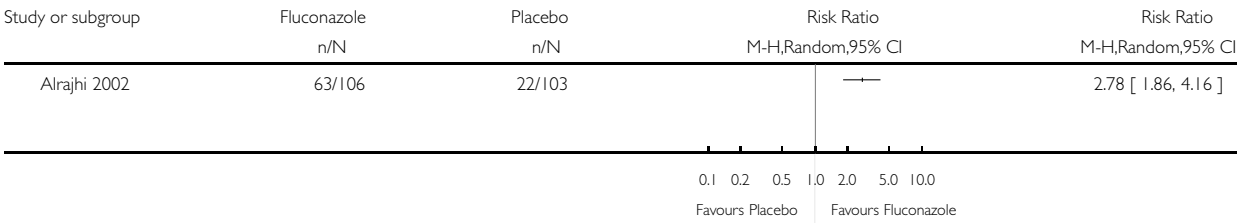


**Analysis 4.1. Comparison 4 Fluconazole (200mg for 6 weeks) *versus* placebo in *L.major*; FU: 3 months, Outcome 1 Complete cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 4 Fluconazole (200mg for 6 weeks) ***versus*** placebo in ***L.major***; FU: 3 months

Outcome: 1 Complete cure

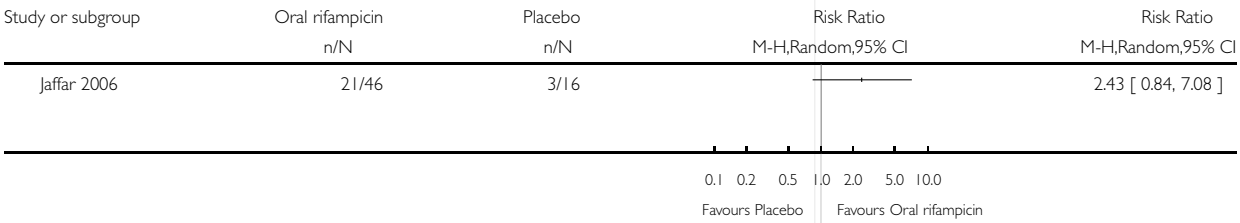



**Analysis 5.1. Comparison 5 Oral rifampicin 10 mg/kg/d TD for 4 to 6 weeks versus placebo; FU: 3 months, Outcome 1 Complete cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 5 Oral rifampicin 10 mg/kg/d TD for 4 to 6 weeks versus placebo; FU: 3 months

Outcome: 1 Complete cure



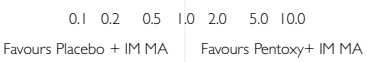
**Analysis 6.1. Comparison 6 IMMA plus oral pentoxifylline *versus* IMMA plus placebo for 20 days in *L. major*; FU: 3 months , Outcome 1 Complete cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 6 IMMA plus oral pentoxifylline ***versus*** IMMA plus placebo for 20 days in ***L. major***; FU: 3 months

Outcome: 1 Complete cure

| Study or subgroup | Oral pentoxyfilline+IM MA<br>n/N | Placebo+IM MA<br>n/N | Risk Ratio<br>M-H,Random,95% CI | Risk Ratio<br>M-H,Random,95% CI |
|---|---|---|---|---|
| Sadeghian 2006 | 26/32 | 16/32 | | 1.63 [ 1.11, 2.39 ] |



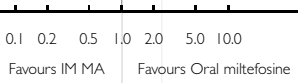

**Analysis 7.1. Comparison 7 Oral miltefosine for 28 days *versus* IMMA for 14 days in *L. major*; FU: 3 months, Outcome 1 Complete cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 7 Oral miltefosine for 28 days ***versus*** IMMA for 14 days in ***L. major***; FU: 3 months

Outcome: 1 Complete cure

| Study or subgroup | Oral miltefosine<br>n/N | IMMA<br>n/N | Risk Ratio<br>M-H,Random,95% CI | Risk Ratio<br>M-H,Random,95% CI |
|---|---|---|---|---|
| Mohebali 2007 | 26/32 | 25/31 | | 1.01 [ 0.79, 1.28 ] |



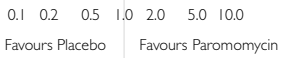
**Analysis 8.1. Comparison 8 Paromomycin (15% + 10% urea twice daily for 14 days) *versus* placebo (twice daily for 14 days) mainly in *L. major*; FU: 2.5 months, Outcome 1 Complete cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 8 Paromomycin (15% + 10% urea twice daily for 14 days) *versus* placebo (twice daily for 14 days) mainly in *L. major*; FU: 2.5 months

Outcome: 1 Complete cure

| Study or subgroup | Paromomycin n/N | Placebo n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Asilian 1995 | 80/126 | 79/125 | | 68.1 % | 1.00 [ 0.83, 1.21 ] |
| Ben- Salah 1995 | 40/66 | 40/66 | | 31.9 % | 1.00 [ 0.76, 1.32 ] |
| **Total (95% CI)** | **192** | **191** | | **100.0 %** | **1.00 [ 0.86, 1.17 ]** |
| Total events: 120 (Paromomycin), 119 (Placebo) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 0.04 (P = 0.97) | | | | | |




**Analysis 8.2. Comparison 8 Paromomycin (15% + 10% urea twice daily for 14 days) *versus* placebo (twice daily for 14 days) mainly in *L. major*; FU: 2.5 months, Outcome 2 Parasitological cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 8 Paromomycin (15% + 10% urea twice daily for 14 days) *versus* placebo (twice daily for 14 days) mainly in *L. major*; FU: 2.5 months

Outcome: 2 Parasitological cure

| Study or subgroup | Paromomycin n/N | Placebo n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Asilian 1995 | 109/126 | 99/125 | | 1.09 [ 0.98, 1.22 ] |

## Analysis 9.1. Comparison 9 Paromomycin (15% + 12% MBCL twice daily x 28 days) *versus* placebo (twice daily for 28 days) in *L. major*; FU: 2 months, Outcome 1 Complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 9 Paromomycin (15% + 12% MBCL twice daily x 28 days) ***versus*** placebo (twice daily for 28 days) in ***L. major***; FU: 2 months

Outcome: 1 Complete cure

| Study or subgroup | Paromomycin n/N | Placebo n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Asilian 2006 | 14/34 | 4/30 | | 3.09 [ 1.14, 8.37 ] |

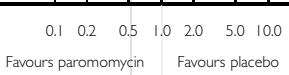

## Analysis 9.2. Comparison 9 Paromomycin (15% + 12% MBCL twice daily x 28 days) *versus* placebo (twice daily for 28 days) in *L. major*; FU: 2 months, Outcome 2 Prevention of scarring.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 9 Paromomycin (15% + 12% MBCL twice daily x 28 days) ***versus*** placebo (twice daily for 28 days) in ***L. major***; FU: 2 months

Outcome: 2 Prevention of scarring

| Study or subgroup | Favours Paromomycin n/N | Favours placebo n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Asilian 2006 | 8/34 | 3/30 | | 2.35 [ 0.69, 8.07 ] |



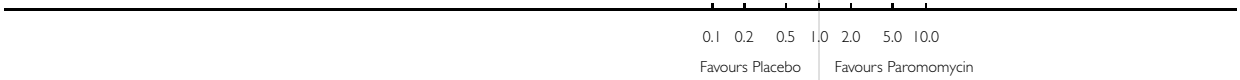
**Analysis 9.3. Comparison 9 Paromomycin (15% + 12% MBCL twice daily x 28 days) *versus* placebo (twice daily for 28 days) in *L. major*; FU: 2 months, Outcome 3 Parasitological cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 9 Paromomycin (15% + 12% MBCL twice daily x 28 days) ***versus*** placebo (twice daily for 28 days) in ***L. major***; FU: 2 months

Outcome: 3 Parasitological cure

| Study or subgroup | Paromomycin n/N | Placebo n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Asilian 2006 | 22/34 | 6/30 | | 3.24 [ 1.52, 6.90 ] |




**Analysis 10.1. Comparison 10 Paromomycin (15%+ 12% MBCL twice daily x 28 days) *versus* PDT (weekly for 4 weeks) in *L. major*; FU: 2 months, Outcome 1 Complete cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 10 Paromomycin (15%+ 12% MBCL twice daily x 28 days) ***versus*** PDT (weekly for 4 weeks) in ***L. major***; FU: 2 months

Outcome: 1 Complete cure

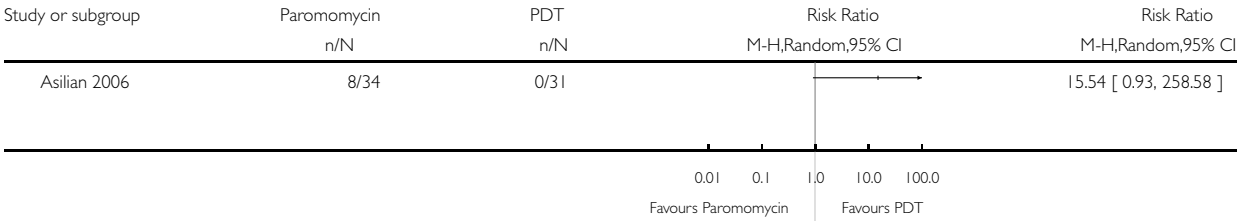
| Study or subgroup | Paromomycin n/N | PDT n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Asilian 2006 | 14/34 | 29/31 | | 0.44 [ 0.29, 0.66 ] |

### Analysis 10.2. Comparison 10 Paromomycin (15%+ 12% MBCL twice daily x 28 days) *versus* PDT (weekly for 4 weeks) in *L. major*; FU: 2 months, Outcome 2 Prevention of scarring.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 10 Paromomycin (15%+ 12% MBCL twice daily x 28 days) ***versus*** PDT (weekly for 4 weeks) in *L. major*; FU: 2 months

Outcome: 2 Prevention of scarring

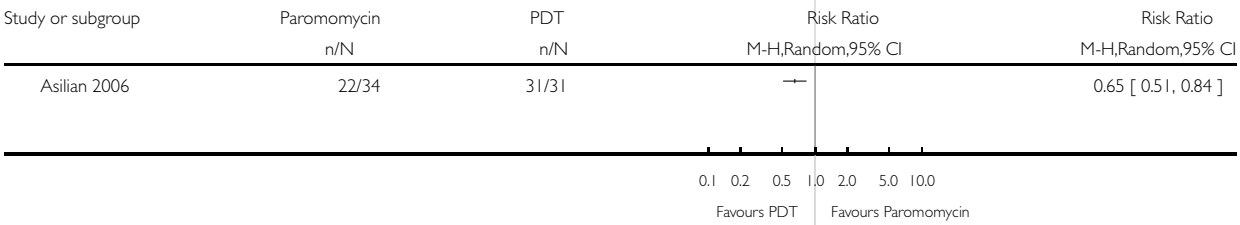



### Analysis 10.3. Comparison 10 Paromomycin (15%+ 12% MBCL twice daily x 28 days) *versus* PDT (weekly for 4 weeks) in *L. major*; FU: 2 months, Outcome 3 Parasitological cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 10 Paromomycin (15%+ 12% MBCL twice daily x 28 days) ***versus*** PDT (weekly for 4 weeks) in *L. major*; FU: 2 months

Outcome: 3 Parasitological cure



**Analysis 11.1. Comparison 11 Paromomycin (4 weeks) *versus* paromomycin (2 weeks) + placebo (2 weeks) in *L. major*; FU: 2.5 months, Outcome 1 Complete cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 11 Paromomycin (4 weeks) ***versus*** paromomycin (2 weeks) + placebo (2 weeks) in *L. major*; FU: 2.5 months

Outcome: 1 Complete cure

| Study or subgroup | Paromomycin (4wks) n/N | Paromomycin (2wks) n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Asilian 2003 | 58/117 | 43/116 | | 1.34 [ 0.99, 1.80 ] |


**Analysis 11.2. Comparison 11 Paromomycin (4 weeks) *versus* paromomycin (2 weeks) + placebo (2 weeks) in *L. major*; FU: 2.5 months, Outcome 2 Parasitological cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 11 Paromomycin (4 weeks) ***versus*** paromomycin (2 weeks) + placebo (2 weeks) in *L. major*; FU: 2.5 months

Outcome: 2 Parasitological cure

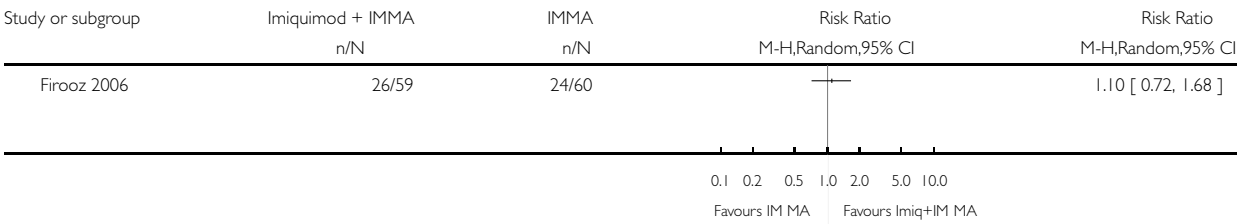
| Study or subgroup | Paromomycin (4 wks) n/N | Paromomycin (2 wks) n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Asilian 2003 | 49/117 | 33/116 | | 1.47 [ 1.03, 2.11 ] |

**Analysis 12.1. Comparison 12 Imiquimod (5% 3 times/week x 28 d) + IMMA (20 mg/kg/d x 14 d) *versus* placebo + i.m. MA in *L.tropica*; FU: 3.5 months, Outcome 1 Complete cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 12 Imiquimod (5% 3 times/week x 28 d) + IMMA (20 mg/kg/d x 14 d) ***versus*** placebo + i.m. MA in ***L.tropica***; FU: 3.5 months

Outcome: 1 Complete cure

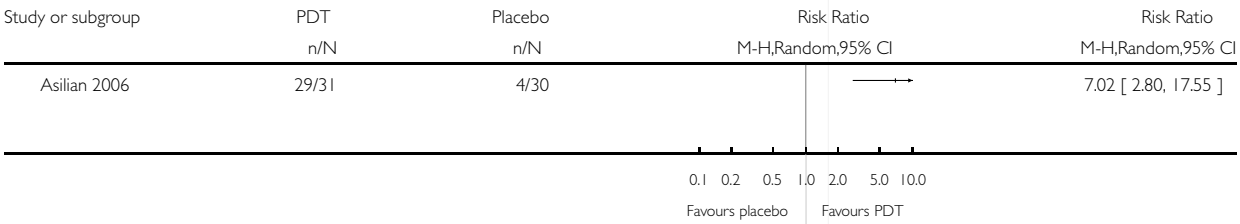



**Analysis 13.1. Comparison 13 PDT (weekly for 4 weeks) *versus* placebo in *L. major*: FU: 2.5 months, Outcome 1 Complete cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 13 PDT (weekly for 4 weeks) ***versus*** placebo in ***L. major***: FU: 2.5 months

Outcome: 1 Complete cure



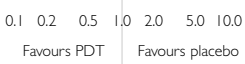
### Analysis 13.2. Comparison 13 PDT (weekly for 4 weeks) *versus* placebo in *L. major*: FU: 2.5 months, Outcome 2 Prevention of scarring.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 13 PDT (weekly for 4 weeks) *versus* placebo in *L. major*: FU: 2.5 months

Outcome: 2 Prevention of scarring

| Study or subgroup | PDT n/N | Placebo n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Asilian 2006 | 0/31 | 3/30 | | 0.14 [ 0.01, 2.57 ] |



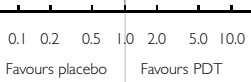

### Analysis 13.3. Comparison 13 PDT (weekly for 4 weeks) *versus* placebo in *L. major*: FU: 2.5 months, Outcome 3 Parasitological cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 13 PDT (weekly for 4 weeks) *versus* placebo in *L. major*: FU: 2.5 months

Outcome: 3 Parasitological cure

| Study or subgroup | PDT n/N | Placebo n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Asilian 2006 | 31/31 | 6/30 | | 4.69 [ 2.37, 9.31 ] |



## Analysis 14.1. Comparison 14 Heat *versus* ILMA once a week for 4 weeks: FU: 6 months, Outcome 1 Complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 14 Heat *versus* ILMA once a week for 4 weeks: FU: 6 months

Outcome: 1 Complete cure

| Study or subgroup | Heat n/N | ILMA n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| 1 Lesions | | | | |
| Sadeghian 2007 | 67/83 | 52/94 | | 1.46 [ 1.18, 1.80 ] |
| 2 Participants | | | | |
| Sadeghian 2007 | 46/57 | 34/60 | | 1.42 [ 1.10, 1.84 ] |


Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 14 Heat *versus* ILMA once a week for 4 weeks: FU: 6 months

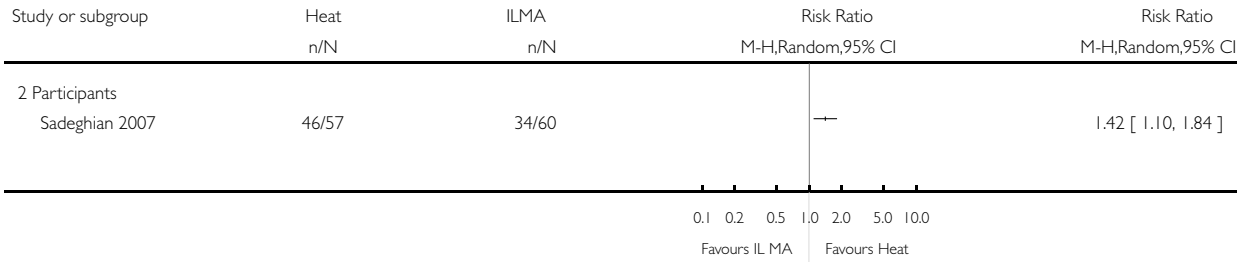
Outcome: 1 Complete cure

| Study or subgroup | Heat n/N | ILMA n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| 1 Lesions | | | | |
| Sadeghian 2007 | 67/83 | 52/94 | | 1.46 [ 1.18, 1.80 ] |

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 14 Heat *versus* ILMA once a week for 4 weeks: FU: 6 months

Outcome: 1 Complete cure

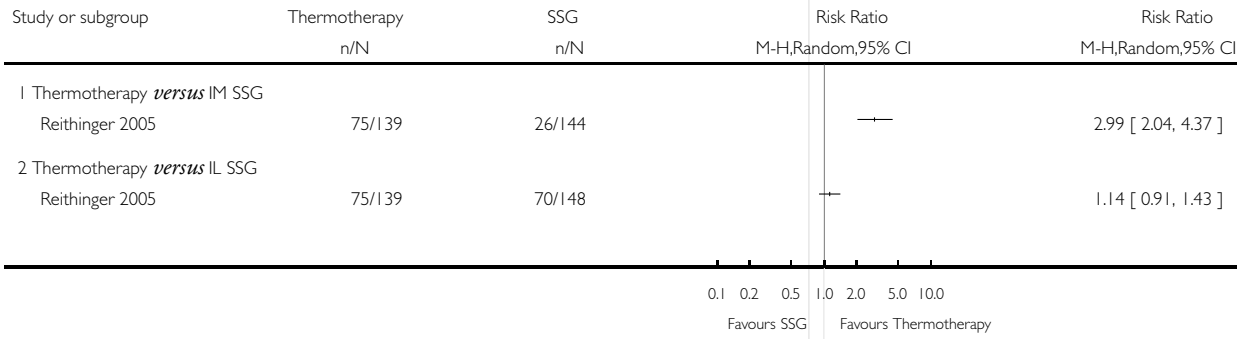



**Analysis 15.1. Comparison 15 Thermotherapy *versus* IM and IL SSG in *L. tropica*; FU: 2 months, Outcome 1 Complete cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 15 Thermotherapy *versus* IM and IL SSG in *L. tropica*; FU: 2 months

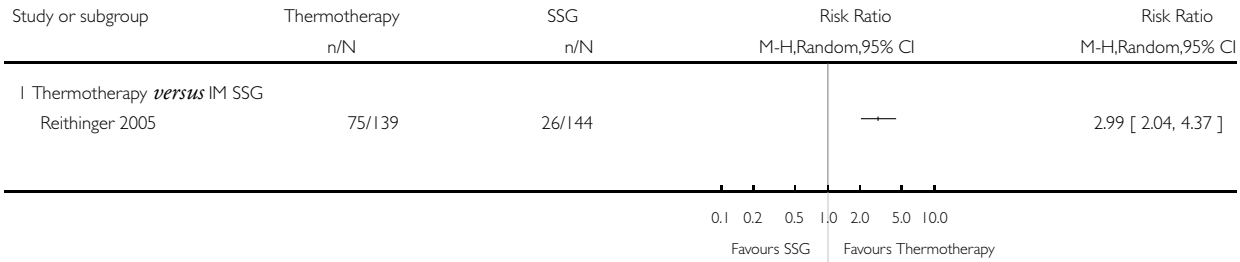
Outcome: 1 Complete cure



Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 15 Thermotherapy *versus* IM and IL SSG in *L. tropica*; FU: 2 months

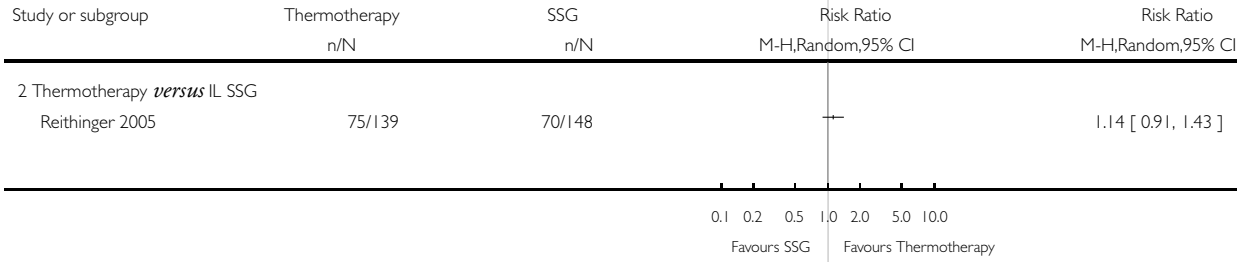
Outcome: 1 Complete cure




Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 15 Thermotherapy *versus* IM and IL SSG in *L. tropica*; FU: 2 months

Outcome: 1 Complete cure

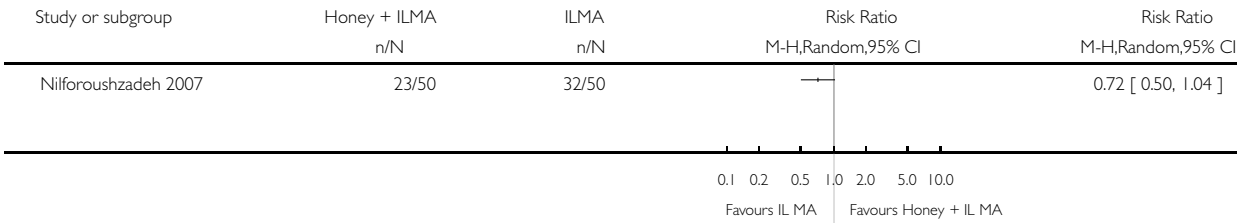


**Analysis 16.1. Comparison 16 Topical honey plus ILMA *versus* ILMA ; FU: 2.5 to 3 months, Outcome 1 Complete cure.**

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 16 Topical honey plus ILMA *versus* ILMA ; FU: 2.5 to 3 months

Outcome: 1 Complete cure




# APPENDICES

## Appendix 1. MEDLINE (OVID) Search Strategy

1. RANDOMIZED CONTROLLED TRIAL.pt.
2. CONTROLLED CLINICAL TRIAL.pt.
3. RANDOMIZED CONTROLLED TRIALS.mp.
4. RANDOM ALLOCATION.mp.
5. DOUBLE BLIND METHOD.sh.
6. SINGLE-BLIND METHOD.sh.
7. or/1-6
8. animal/ not human/
9. 7 not 8
10. CLINICAL TRIAL.pt.
11. CLINICAL TRIALS.mp.
12. (clin$ adj25 trial$).ti,ab.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
14. PLACEBOS.sh.
15. placebo$.ti,ab.
16. random$.ti,ab.
17. RESEARCH DESIGN.sh.
18. or/10-17
19. 18 not 8
20. 19 not 9
21. COMPARATIVE STUDY.pt.
22. EVALUATION STUDIES.mp.
23. FOLLOW UP STUDIES.sh.
24. PROSPECTIVE STUDIES.sh.
25. (control$ or prospectiv$ or volunteer$).ti,ab.
26. or/21-25
27. 26 not 8
28. 27 not (9 or 20)
29. 9 or 20 or 28
30. exp Leishmaniasis, Cutaneous/
31. (solitary or limited or old world or localised).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

32. 30 and 31
33. 29 and 32
34. limit 33 to yr="2003 - 2007"

## Appendix 2. EMBASE (OVID) 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. cutaneous leishmaniasis.mp. or Skin Leishmaniasis/
15. (solitary or limited or old world or localised).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
16. 14 and 15
17. 13 and 16
18. limit 17 to yr="2005 - 2007"

## Appendix 3. CINAHL Search Strategy

(modified from the SIGN Search Filters www.sign.ac.uk/methodology/filters)
1. cutaneous leishmaniasis.mp.
2. (solitary or limited or old world or localised).mp. [mp=title, subject heading word, abstract, instrumentation]
3. 1 and 2
4. exp clinical trials/
5. Clinical trial.pt.
6. (clinic$ adj trial$1).tw.
7. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw.
8. Randomi?ed control$ trial$.tw.
9. Random assignment/
10. Random$ allocat$.tw.
11. Placebo$.tw.
12. Placebos/
13. Quantitative studies/
14. Allocat$ random$.tw.
15. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 3 and 15

## Appendix 4. 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$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Words] and (cutaneous and leishmaniasis) or (cutanea and leishmaniosis) or (old and world and leishman$) or ((solitar$ or locali$ or limited) and leishman$) [Words]

## Appendix 5. Adverse Effects Search Strategy in MEDLINE

1. exp product surveillance, postmarketing/ or exp adverse drug reaction reporting systems/ or exp clinical trials, phase iv/
2. adverse events.mp.
3. adverse effects.mp.
4. exp hypersensitivity/ or exp drug hypersensitivity/ or exp drug eruptions/ or exp hypersensitivity, delayed/ or exp hypersensitivity, immediate/
5. exp hypersensitivity, immediate/ or exp anaphylaxis/ or exp conjunctivitis, allergic/ or exp dermatitis, atopic/ or exp food hypersensitivity/ or exp respiratory hypersensitivity/ or exp urticaria/
6. side effect$.mp.
7. exp Poisoning/
8. exp Substance-Related Disorders/
9. exp Drug Toxicity/
10. exp Abnormalities, Drug-Induced/
11. exp Teratogens/
12. exp Mutagens/
13. exp Carcinogens/
14. exp dermatitis, contact/ or exp dermatitis, allergic contact/ or exp dermatitis, irritant/ or exp dermatitis, phototoxic/
15. photoallergic reactions.mp.
16. exp dermatitis, allergic contact/ or exp dermatitis, photoallergic/
17. sensitization.mp.
18. fetal abnormalities.mp.
19. exp Drug Monitoring/
20. harm$ effects.mp.
21. (toxic effects or drug effects).mp.
22. undesirable effect$.mp.
23. (safe or safety).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
24. toxicity.mp.
25. noxious.mp.
26. serious reaction$.mp.
27. complication$.mp.
28. tolerability.mp.
29. (adverse adj3 (effect$ or reaction$ or event$ or outcome$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
30. Tachyphylaxis/ci, de [Chemically Induced, Drug Effects]
31. *Itraconazole/
32. *Ketoconazole/
33. *Paromomycin/
34. *Allopurinol/
35. *Amphotericin B/
36. aminosidine sulphate.mp.
37. pentamidine isethionate.mp. or *Pentamidine/
38. *Aminoglycosides/

39. miltefosine.mp.
40. thermotherapy.mp.
41. *Granulocyte-Macrophage Colony-Stimulating Factor/
42. *Mefloquine/
43. *Immunotherapy/
44. *BCG Vaccine/ or bacillus calmette guerin.mp.
45. *Meglumine/
46. sodium stibogluconate.mp.
47. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
48. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
49. 47 and 48
50. (solitary or limited or old world or localised).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
51. cutaneous leishmaniasis.mp. or exp Leishmaniasis, Cutaneous/
52. 50 and 51
53. 49 and 52

## WHAT'S NEW

Last assessed as up-to-date: 30 March 2008.

| | | |
|---|---|---|
| 18 April 2008 | Amended | Converted to new review format. |

## HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 4, 2008

| | | |
|---|---|---|
| 21 December 2007 | New citation required and conclusions have changed | Substantive amendment |

## CONTRIBUTIONS OF AUTHORS

Link with editorial base and co-ordinate contributions from co-reviewers (UG)

Searching for trials (includes developing a search strategy, obtaining papers, contacting authors, investigators or drug companies) (UG, MP, LR)

Selecting which trials to include and extracting data from trials (MC, UG, MP, LR)

Enter data into RevMan (MP)

Carry out analysis (UG, MP)

Interpret data (UG, MP)

Draft final review (contribution from all)

The expert representative (JA) focused on relevance and applicability of the review

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- Spanish Society of Dermatology and Venereology and Evidence-Based Dermatology (SEDE-DBE), Spain.
- Hospital Plató, c/ Plató 21 08006 Barcelona, Spain.

### External sources

- Office of Control of Neglected Tropical Diseases (WHO/CDS/NTD/IDM), Communicable Disease Cluster, World Health Organization, Switzerland.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol of this review was first entitled "Interventions for solitary or limited cutaneous leishmaniasis". However, we decided to split this subject into two reviews. We have amended the title of this review to "Interventions for Old World cutaneous leishmaniasis". We have also published a Cochrane protocol entitled "Interventions for American cutaneous and mucocutaneous leishmaniasis" (Gonzalez 2004). We did this because the *Leishmania* species in the geographical areas involving the Old World differ from the ones affecting the New World. Due to the title change and also in response to referee comments, we have modified the Background considerably. Also our Objectives have focused on the localised form of CL in the Old World rather than the solitary or limited form of CL.

In the Methods section, we have modified "types of participants" to 'immunocompetent people who have localised OWCL'; we have added a list of interventions under "types of interventions" in response to referees comments and to ease readability and also following advice from the referees under "types of outcome measures" we have clarified the primary outcomes and we added a phrase to define emergence of resistance to the tertiary outcomes.