REVIEW ARTICLE

Safety and efficacy of current alternatives in the topical treatment of cutaneous leishmaniasis: a systematic review

PRISCILA WOLF NASSIF[1], TATIANE FRANÇA PERLES DE MELLO[2], TAÍSA ROCHA NAVASCONI[1], CAMILA ALVES MOTA[2], IZABEL GALHARDO DEMARCHI[1], SANDRA MARA ALESSI ARISTIDES[3], MARIA VALDRINEZ CAMPANA LONARDONI[3], JORGE JUAREZ VIEIRA TEIXEIRA[3] *and* THAÍS GOMES VERZIGNASSI SILVEIRA[3]*

[1] *Graduate Program in Health Sciences, State University Maringa, Avenida Colombo, 5790, Jardim Universitário, CEP 87020-900, Maringá, Paraná, Brazil*
[2] *Graduate Program in Bioscience and Physiopathology, State University Maringa, Avenida Colombo, 5790, Jardim Universitário, CEP 87020-900, Maringá, Paraná, Brazil*
[3] *Department of Clinical Analysis and Biomedicine, State University Maringa, Avenida Colombo, 5790, Jardim Universitário, CEP 87020-900, Maringá, Paraná, Brazil*

(*Received 2 December 2016; revised 22 February 2017; accepted 24 February 2017; first published online 3 April 2017*)

SUMMARY

Studies of topical treatments for leishmaniasis were systematically reviewed, to evaluate the therapeutic efficacy, safety and any adverse effects of these treatments. The papers identified in the databases PubMed and Web of Knowledge involved eight studies with a total of 1744 patients. The majority of trials was from Iran (4/8), covered a period of 8 years (2003–2011), and included patients 4–85 years of age. The most frequent *Leishmania* species in the studies were *L. tropica* (4/8) and *L. major* (2/8). The treatments administered were thermotherapy, paromomycin and combinations, CO_2 laser, 5-aminolevulinic acid hydrochloride (10%) plus visible red light (633 nm) and cryotherapy. Six articles reported cure rates over 80·0%. Six studies reported on failure rates, three of them reporting rates lower than 10%. Four studies did not report relapses or recurrences, while the other studies reported low rates (1·8–6·3%). The most common adverse effects of the topical treatments were redness/erythema, pain, pruritus burning, oedema, vesicles and hyper- or hypopigmentation. The results provide strong evidence that the treatments topical evaluated showed high cure rates, safety and effectiveness, with low side-effects, relapse and recurrence rates, except for cryotherapy, which showed a moderate cure rate.

Key words: Antiprotozoal agents, leishmaniasis, cutaneous leishmaniasis, *Leishmania*, clinical trials.

INTRODUCTION

Leishmaniasis is caused by parasitic protozoans of the genus *Leishmania*, which are transmitted by the bite of infected sandflies (World Health Organization, 2016). Leishmaniasis is a major health problem throughout the developing world (Miranda-Verastegui *et al*. 2005; Nilforoushzadeh *et al*. 2008) with an estimated 900·000–1·3 million new cases and 20 000–30 000 deaths annually (World Health Organization, 2016). The three main forms of the disease are: visceral leishmaniasis, which is fatal if left untreated; cutaneous leishmaniasis (CL), which is the most common form (0·7–1·3 million new cases worldwide annually are estimated) and causes skin lesions, leaving permanent scars and serious disability; and mucocutaneous leishmaniasis, which leads to partial or total destruction of mucous membranes of the nose, mouth and throat (World Health Organization, 2016).

The pentavalent antimony compounds sodium stibogluconate (ST) and meglumine antimoniate (MA) have been the mainstays of antileishmanial therapy for CL (Santos *et al*. 2004; Miranda-Verastegui *et al*. 2005; Sadeghian and Nilforoushzadeh, 2006; Solomon *et al*. 2007, 2013; Munir *et al*. 2008; Nilforoushzadeh *et al*. 2008; Nascimento *et al*. 2010; Neves *et al*. 2011; Motta and Sampaio, 2012; Trinconi *et al*. 2014). However, treatment with pentavalent antimony is expensive, lengthy, must be administered parenterally or intralesionally, requires many courses of treatment, and is frequently complicated by toxicity (cardiopathy, pancreatitis and renal and hepatic complications) (Santos *et al*. 2004; Miranda-Verastegui *et al*. 2005; Sadeghian and Nilforoushzadeh, 2006; Nilforoushzadeh *et al*. 2008; Nascimento *et al*. 2010; Neves *et al*. 2011; Solomon *et al*. 2013). Amphotericin B and pentamidine (pentavalent antimony) are considered second-line treatments and can cause irreversible toxic effects (nephrotoxicity)

* Corresponding author. Department of Clinical Analysis and Biomedicine, Graduate Program in Health Sciences, State University Maringa, Avenida Colombo, 5790, Jardim Universitário, CEP 87020-900, Maringá, Paraná, Brazil. E-mail: tgvsilveira@uem.br

Parasitology (2017), **144**, 995–1004.
doi:10.1017/S0031182017000385

(Santos *et al*. 2004; Miranda-Verastegui *et al*. 2005; Neves *et al*. 2011; Motta and Sampaio, 2012).

Current therapies for CL are limited by low efficacy, the requirement for prolonged treatment, and increasing development of clinical resistance and recurrence (Miranda-Verastegui *et al*. 2005, 2009; Trinconi *et al*. 2014; World Health Organization, 2016). New drugs and different therapeutic regimens have been evaluated. Many investigators have attempted to find an appropriate, highly effective oral or topical treatment with relatively minor adverse effects (Nilforoushzadeh *et al*. 2008).

The aim of this systematic review was to explore new topical treatment options for CL, evaluate their reported therapeutic efficacy and safety, and describe their adverse effects.

METHODS

Literature search

A systematic literature review was conducted in the PubMed and Web of Knowledge databases, covering the period from 11 July 2004 to 8 July 2014. The methodology was defined by the PRISMA statement (Preferred Reporting of Systematic Reviews and Meta-Analysis) (Shamseer *et al*. 2015) (Fig. 1).

In the first phase of the study, four researchers (TRN, TFPM, CAM and PWN) conducted the search and screened the titles and abstracts. To recover publications in PubMed, we used MeSH (Medical Subject Headings) terms. The four researchers conducted searches independently, to define the number of MeSH terms. Any disagreements were resolved by consensus. The MeSH terms were validated by two experts (JVT, TGVS). The MeSH terms were organized into three groups: group 1, 'antiprotozoal agents' OR 'drug therapy' OR 'treatment outcome' OR 'complementary therapies' OR 'photochemotherapy' OR 'anti-infective agents' OR 'medication therapy management' OR 'organometallic compounds/chemistry' AND group 2, 'leishmaniasis, mucocutaneous' OR 'leishmaniasis' OR 'leishmaniasis, cutaneous' OR 'leishmania' AND group 3, 'clinical trial'. The Web of Knowledge was searched by topic, which ensures good sensitivity.

Study selection

Inclusion criteria. Publications that describe a topical treatment for CL, independently of the clinical stage of the disease, were initially included in the study. Only original research, in English, and with a summary available was included.

Exclusion criteria. Reviews, case reports, comments to the editor, letters, interviews, guidelines and errata were excluded.

Quality assessment. For the second phase, the full text of papers was randomly distributed to the researchers of group 1. In the case of disagreement, the inclusion or exclusion of the paper was decided by consensus. In the third phase, the papers selected by group 1 were distributed to four independent evaluators (TGVS, MVCL, SMAA and IGD – group 2) for certification. The final selection of publications was done by consensus among the researchers of both groups. The only articles remaining were those whose authors used statistical methods for data analysis and included the clinical protocol criteria, such as efficacy and safety, and reported the positive or negative results of the treatment. Additional references from the original articles were surveyed in order to identify other publications of interest.

Data extraction. In the fourth phase, the researchers from group 1, with the support of two experts (JJVT and TGVS), organized the structure of the topics to compose the tables. Table 1 (study, country, design, period of study, age range or mean in years, gender, patients enrolled, statistics), Table 2 (study, *Leishmania* species, treatments, number of patients who completed the treatment, clinically cured '%' patients or lesions, therapy failure '%', relapse or recurrence '%'), Table 3 (treatments, adverse effects '%', study) and Table 4 (therapy, dose, administration/time, efficacy, safety). The articles were distributed to researchers from group 1 to complete the tables of findings, and the entries were checked by the group 2 researchers. The term 'efficacy' or variations, described in Table 4, was classified in the table as described by the authors of the studies. All numbers recorded in Table 2 are 'per-protocol'. Relapse was reported as reappearance of the lesion after complete healing. Some authors considered relapse as therapeutic failure.

RESULTS AND DISCUSSION

Literature review

CL is endemic worldwide. About 95% of CL cases occur in the Americas, the Mediterranean basin, the Middle East and Central Asia. Over two-thirds of new CL cases occur in six countries: Afghanistan, Algeria, Brazil, Colombia, the Islamic Republic of Iran and the Syrian Arab Republic (World Health Organization, 2016). In the Old World, CL is caused by five species of *Leishmania: L. infantum, L. tropica, L. major, L. aethiopica* and *L. donovani*. In the New World, CL is caused by several species of the subgenera *Leishmania* and *Viannia*, mainly *L. amazonensis, L. mexicana, L. braziliensis, L. guyanensis* and *L. panamensis* (World Health Organization, 2010). Efficacy rates of CL treatments are difficult to interpret. The

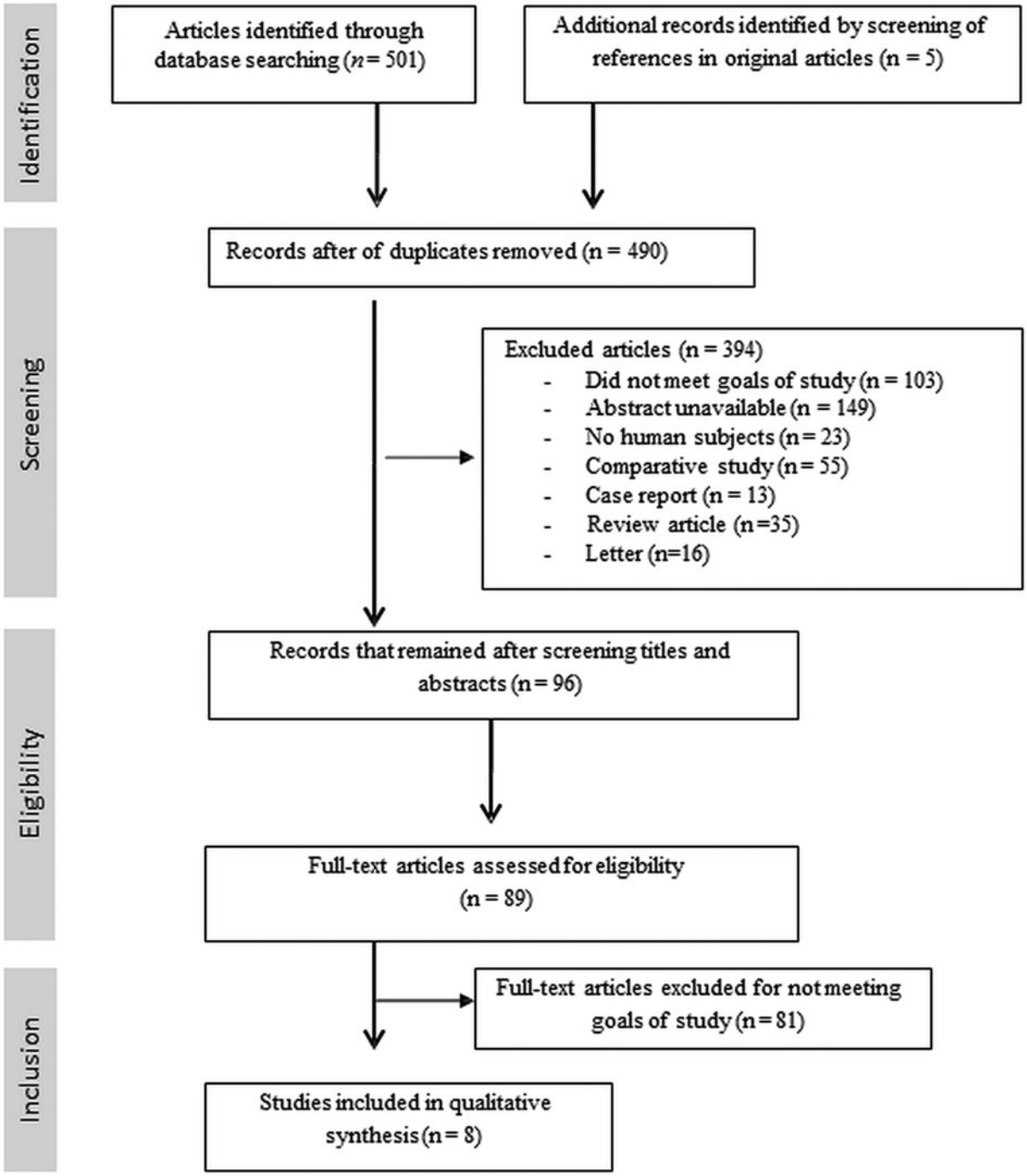

Fig. 1. Flow diagram of study selection for the systematic review.

geographical variation in efficacy and the additional variation in the susceptibility of *Leishmania* species are high. For instance, Cota *et al*. (2016) found a significantly lower spontaneous cure rate for *L. braziliensis* infection (6·4%) than for *L. mexicana* (44%), in addition to a 20% relapse rate in patients with initial healing. CL is by nature a self-healing disease, and treatment may only accelerate the healing process (Dorlo *et al*. 2012).

In this systematic review, we initially identified 350 articles in the PubMed and 151 in the Web of Knowledge databases. The final systematic review involved eight studies with 1744 patients (Fig. 1), in accordance with the PRISMA statement. Studies were considered regardless of the stage of leishmaniasis treated, and included several treatment regimens.

Characteristics of studies and patients

The largest number of studies were conducted in Iran (four of eight), followed by Afghanistan (two of eight). All were clinical trials, published during an 8-year period (2003–2011), and covered patients 4–85 years of age; overall, 51·5% of the subjects were females (Arana *et al*. 2001; Asilian *et al*. 2004*b*; Reithinger *et al*. 2005; Asilian and Davami,

Table 1. Baseline characteristics of clinical trials included in the analysis of new perspectives in the treatment of cutaneous leishmaniasis

Study	Country	Design	Period of study	Age range or mean (years)	Gender (%)	Patients enrolled	Statistics
Asilian *et al.* (2004*a*, *b*)	Iran	Clinical trial	NR	12–60	M 40·8 F 59·2	233	Yes
Asilian and Davami (2006)	Iran	Clinical trial	9/2004–5/2005	5–59	M 45·6 F 54·4	57	Yes
Ben Salah *et al.* (2013)	Tunisia	Clinical trial, phase III	1/2008–7/2011	5–65	M 51·0 F 49·0	375	Yes
Bumb *et al.* (2013)	India	Clinical trial, phase IV open-label	6/2009–12/2010	4–85	M 47·0 F 53·0	100	Yes
Layegh *et al.* (2009)	Iran	Clinical trial	9/2006–6/2007	G1 < 13, mean 6·2 G2 < 13, mean 6·8	M 48·1 F 51·9	79	Yes
Reithinger *et al.* (2005)	Afghanistan	Clinical trial	1/2003–9/2003	>5	M 49·9 F 50·1	401	Yes
Sadeghian *et al.* (2007)	Iran	Clinical trial	NR	>5	M 56·4 F 43·6	117	Yes
Safi *et al.* (2012)	Afghanistan	Clinical trial	NR	5–75	M 46·3 F 53·7	382	Yes

NR (not reported), G1 (Group 1), G2 (Group 2), M (male), F (female).

2006; Layegh *et al.* 2009; Safi *et al.* 2012; Ben Salah *et al.* 2013; Bumb *et al.* 2013) (Table 1).

The most frequent *Leishmania* species were *L. tropica* (four of eight) and *L. major* (two of eight) (Table 2). The treatments administered were thermotherapy, paromomycin (PR) and combinations, CO_2 laser, photodynamic therapy (PDT) and cryotherapy. A mean of 190·1 patients completed the studies. Most papers addressed the cure rates, regardless of the number of lesions, while some reported the numbers of both treated and healed lesions. Most studies evaluated healing after 3 months (three articles) (Asilian *et al.* 2004*b*; Reithinger *et al.* 2005; Asilian and Davami, 2006) or 6 months (three articles) (Sadeghian *et al.* 2007; Safi *et al.* 2012; Bumb *et al.* 2013).

Six articles reported cure rates over 80% (Asilian *et al.* 2004*b*; Asilian and Davami, 2006; Sadeghian *et al.* 2007; Safi *et al.* 2012; Ben Salah *et al.* 2013; Bumb *et al.* 2013); two of them after a 3-month follow-up period (Armijos *et al.* 2004; Asilian *et al.* 2004*b*) and three after 6 months (Asilian *et al.* 2004*b*; Sadeghian *et al.* 2007; Bumb *et al.* 2013). Six studies reported failure rates, three of them lower than 10% (Armijos *et al.* 2004; Asilian *et al.* 2004*b*; Bumb *et al.* 2013). Four articles reported no recurrences after the treatments (Reithinger *et al.* 2005; Sadeghian *et al.* 2007; Layegh *et al.* 2009; Bumb *et al.* 2013), and three studies did not report the recurrence rate (Asilian and Davami, 2006; Asilian *et al.* 2004*b*; Safi *et al.* 2012), while the remaining studies reported low rates (1·8–6·3%).

The most common adverse effects of topical treatments were redness/erythema, pain, pruritus, burning, oedema, vesicles and hyper- or hypopigmentation (Armijos *et al.* 2004; Asilian *et al.* 2004*b*; Reithinger *et al.* 2005; Sadeghian *et al.* 2007; Layegh *et al.* 2009; Safi *et al.* 2012; Ben Salah *et al.* 2013; Bumb *et al.* 2013) (Table 3).

Data on administration and treatment time for the treatments that were classified as 'Efficacious' and as having 'Acceptable risk with monitoring' are listed in Table 4. PR and combinations, PDT, cryotherapy and thermotherapy were all considered 'Clinically useful treatments' (Reithinger *et al.* 2005; Asilian and Davami, 2006; Sadeghian *et al.* 2007; Layegh *et al.* 2009; Safi *et al.* 2012; Ben Salah *et al.* 2013; Bumb *et al.* 2013). Only CO_2 laser was classified as a 'Possibly useful treatment' (Asilian *et al.* 2004*b*).

Thermotherapy/heat therapy was applied in one to four weekly sessions. PR and combinations were evaluated in twice-daily applications for 20 days. CO_2 laser, cryotherapy and PDT were administered by local application once a week, for a total of one to six sessions.

The risk of bias in individual studies was discussed by Reithinger *et al.* (2005), Layegh *et al.* (2009) and Safi *et al.* (2012).

Table 2. Characteristics of clinics, therapeutics and epidemiological of clinical trials included in the study

Study	*Leishmania* species	Treatments	Patients that completed the treatment	Clinically cured (%) (patients or lesions)[a]	Therapy failure (%)	Relapse or recurrence (%)
Asilian *et al*. (2004*a*, *b*)	NR	G1 (Laser CO_2)	83 (111 lesions)	93·7 (3 months AE) lesion	6·3 (3 months AE)	6·3 (1 month AE)
		G2 (MA)	91 (210 lesions)	83·8 (90 days AS) lesion	16·2 (90 days AS)	NR
Asilian and Davami (2006)	*L. major*	G1 (ALA–PDT)	20 (31 lesions)	93·5 (90 days AS)[b]	0·0 (90 days AS)	NR
		G2 (PR–MBCL)	19 (34 lesions)	41·2 (90 days AS)[c]	29·4 (90 days AS)	NR
		G3 (Placebo)	18 (30 lesions)	13·3 (90 days AS)[d]	46·7 (90 days AS)	NR
Ben Salah *et al*. (2013)	*L. major*	G1 (PR–GE)	124	81·5 (42 days AS)	15·3 (42 days AS)	3·2 (42 days AS)
		G2 (PR)	122	83·6 (42 days AS)	13·1 (42 days AS)	3·3 (42 days AS)
		G3 (Vehicle control)	114	64·0 (42 days AS)	34·2 (42 days AS)	1·8 (42 days AS)
Bumb *et al*. (2013)	*L. tropica*	G1 (Radiofrequency-induced heat therapy)	50	98 (6 months AE)	2·0 (6 months AE)	0·0 (12 months AE)
		G2 (Intralesional ST)	50	94 (6 months AE)	6·0 (6 months AE)	0·0 (12 months AE)
Layegh *et al*. (2009)	*L. tropica*	G2 (Cryotherapy)	36	NR	58·3 (6 months AE)	0·0 (6 months AE)
		G1 (Intralesional MA)	36	NR	27·7 (6 months AE)	0·0 (6 months AE)
Reithinger *et al*. (2005)	*L. tropica*	G1 (Thermotherapy)	108	69·4 (100 days AS)	NR	0·0 (100 days AS)
		G2 (Intralesional ST)	93	75·3 (100 days AS)	NR	0·0 (100 days AS)
		G3 (Intramuscular ST)	58	44·8 (100 days AS)	NR	0·0 (100 days AS)
Sadeghian *et al*. (2007)	NR	G1 (Radiofrequency-induced heat therapy)	57	80·7 (6 months AE)	19·3 (6 months AE)	0·0 (6 months AE)
		G2 (MA)	60	56·7 (6 months AE)	43·3 (6 months AE)	0·0 (6 months AE)
Safi *et al*. (2012)	*L. tropica*	G1 (Thermotherapy)	189	82·5 (6 months AE)	NR	NR
		G2 (MA)	193	74·0 (6 months AE)	NR	NR

[a] Per protocol, PR (15% paromomycin), PR–GE (15% paromomycin plus 0·5% gentamicin), PR–MBCL (15% paromomycin plus 12% methylbenzonium chloride), MA (meglumine antimoniate), ST (sodium stibugluconate), ALA–PDT [*Photodynamic therapy*; 10% 5-aminolevulinic acid hydrochloride plus visible red light (633 nm)], AS (after the start of treatment), AE (after the end of treatment), NR (not reported), G1 (Group 1), G2 (Group 2), G3 (Group 3).
[b] Completely improved end 6·5% partially improved.
[c] Completely improved and 29·4% partially improved.
[d] Completely improved and 40·0% partially improved.

Table 3. Description of adverse effects of the new drugs for the treatment of CL

Treatments	Adverse effects (%)	Study
PR and combination	Pruritus, burning, redness, discharge, oedema and pain, but all were generally mild and tolerable, in some patients	Asilian and Davami (2006)
	Erythema (6); vesicles (26); oedema (3); pain (2); bronchitis (3); upper respiratory tract infection (2); oropharyngeal pain (2); skin irritation (7)	Ben Salah *et al*. (2013)
	Erythema (5); vesicles (21); oedema (2); pain (2); bronchitis (4); paronychia (2); superinfection (2); oropharyngeal pain (3); skin irritation (4)	Ben Salah *et al*. (2013)
Thermotherapy	Secondary infections (1·9); superficial second-degree burns where electrodes were applied	Reithinger *et al*. (2005)
	NR	Safi *et al*. (2012)
	Satellite lesions (1·8)	Sadeghian *et al*. (2007)
	Scarring and hyperpigmentation	Bumb *et al*. (2013)
ALA–PDT	Pruritus, burning, redness, discharge, oedema and pain, but all were generally mild and tolerable, in some patients	Asilian and Davami (2006)
CO_2 laser	Hyperpigmentation, persistent redness (4·5); hypertrophic scarring (6)	Asilian *et al*. (2004*a*, *b*)
Cryotherapy	Erythema and oedema at the site; hypopigmentation (5·5); hyperpigmentation (19·4)	Layegh *et al*. (2009)

PR (15% paromomycin), ALA–PDT [Photodynamic therapy; 10% 5-aminolevulinic acid hydrochloride plus visible red light (633 nm)]; NR, not reported.

Modes of treatment

The World Health Organization and other experts suggest the use of local treatments for CL, because this approach limits the risk of adverse effects, may reduce cost, and may enhance compliance and preserve the efficacy of treatments (El-On *et al*. 1984; Soto *et al*. 2002; Sosa *et al*. 2013).

Paromomycin

PR acts by interfering in the protein synthesis of the *Leishmania* parasite without affecting mammalian cells (Fernández *et al*. 2011). A study conducted in Tunisia, with 15% PR and PR plus 0·5% gentamicin (PR–GE) for CL caused by *L. major* found cure rates of 83·6% for PR and 81·5% for PR–GE (Ben Salah *et al*. 2013). In a similar study of patients with *L. panamensis* from Panama; the cure rate of the index lesion was 87% for PR–GE and 60% for PR; including all treated lesions, and the final cure rates were 94 and 67%, respectively (Sosa *et al*. 2013).

In Iran, PR plus 12% methylbenzethonium chloride (PR–MBCL) was used for CL caused by *L. major*; 41·2% of lesions were healed at 90 days after treatment (Asilian and Davami, 2006). PR–MBCL was also evaluated in Guatemala for CL caused by *L. braziliensis* and *L. mexicana*, with an 85·7% cure rate at the 12-month follow-up (Arana *et al*. 2001), and in Ecuador provided a 79·3% cure rate 12 weeks after treatment (Armijos *et al*. 2004).

The most common adverse effects of PR and combinations were erythema, vesicles, oedema, skin irritation and pain (Arana *et al*. 2001; Armijos *et al*. 2004; Asilian and Davami, 2006; Ben Salah *et al*. 2013; Sosa *et al*. 2013).

PR and combinations are potentially effective for CL treatment, and have acceptable side-effects. However, the efficacy against CL caused by the various species of *Leishmania* remains to be investigated.

Thermotherapy

Laboratory studies have shown that *Leishmania* parasites do not multiply in macrophages at temperatures >39 °C *in vitro*. Thermotherapy promotes the destruction of parasites by heat associated with an immediate collagen contraction with posterior tissue remodelling (Alster and Tanzi, 2004; Alavi-Naini *et al*. 2012). These observations led to studies investigating the efficacy of treatments with heat-generating infrared light, direct-current electrical stimulation, ultrasound and laser light (Reithinger *et al*. 2005). A thermotherapy was applied locally with a portable, battery-operated, localized current field radiofrequency (RF) generator (ThermoMed 1·8; Thermosurgery Technologies).

Thermotherapy was as effective as conventional therapy for small lesions caused by *L. tropica* in Afghanistan. The odds of cure among the patients treated with thermotherapy were 1·65 higher than those for patients treated with MA, although the type of lesion was significantly associated with the treatment outcome (better response in papules < or = 1 cm^2) (Safi *et al*. 2012) with use the of a portable, battery-operated, localized current field RF generator (ThermoMed 1·8; Thermosurgery Technologies, Phoenix, Arizona). However, Reithinger *et al*. (2005) showed that thermotherapy was more efficient (75%) than intramuscular sodium ST (45%). Thermotherapy and intralesional ST for *L. tropica* in India showed similar 6-month cure rates of over 98%, with no relapses after 1 year (Bumb *et al*. 2013) using accurate field RF generator (ThermoMed 1·8; Thermosurgery Inc., Phoenix, AZ, USA).

Table 4. Conclusion on new drugs for the treatment of CL in the systematic review

Therapy	Dose	Administration/time	Efficacy	Safety	Practice/clinical implications	Study
PR and combinations	15% Paromomycin	Topical – twice daily – 20 days	Efficacious	Acceptable risk with monitoring	Clinically useful	Ben Salah *et al*. (2013)
	15% Paromomycin and 0·5% gentamicin	Topical – twice daily – 20 days	Efficacious	Acceptable risk with monitoring	Clinically useful	Ben Salah *et al*. (2013)
Thermotherapy/ heat therapy	One or more consecutive applications of 50 °C for 30 s	Topical – single treatment	Efficacious	Acceptable risk with monitoring	Clinically useful	Reithinger *et al*. (2005)
	Radiofrequency at 50 °C (122°F) for 30 s	Topical – single session	Efficacious	Acceptable risk with monitoring	Clinically useful	Safi *et al*. (2012)
	Radiofrequency at 50 °C for 30 s	Topical – once weekly – 4 weeks	Effective	Acceptable risk with monitoring	Clinically useful	Sadeghian *et al*. (2007)
	Radiofrequency – Thermomed Model 1·8 device – 30–60 s	Topical – 1 session	Efficacious	Acceptable risk with monitoring	Clinically useful	Bumb *et al*. (2013)
CO_2 laser	Pulse width was 0·5–5 s (30 W, continuous) was applied to the lesion and a radius of 2–3 mm around it). The procedure was repeated until the ulcer bed turned brown	Topical – 1 session	Efficacious	Acceptable risk with monitoring	Possibly useful	Asilian *et al*. (2004*a*, *b*)
Cryotherapy	Liquid nitrogen −195 °C (10–15 s), twice per cycle with a thawing interval of 20 s	Topical – weekly – up to 6 weeks	Efficacious	Acceptable risk with monitoring	Clinically useful	Layegh *et al*. (2009)
ALA–PDT	10% 5-aminolaevulinic acid (5-ALA) hydrochloride plus visible red light (633 nm) at 100 J cm^{-2}	Topical (once weekly) – 4 weeks	Efficacious	Acceptable risk with monitoring	Clinically useful	Asilian and Davami (2006)

PR (15% paromomycin), ALA–PDT [*Photodynamic therapy*; 10% 5-aminolevulinic acid hydrochloride plus visible red light (633 nm)].

Thermotherapy also proved to be more efficient than intralesional MA in Iran, with a cure rate of 80·7 *vs* 56·7%, also with no relapses (Sadeghian *et al*. 2007). This procedure was performed with an RF heat generator (4 MHz, maximum Output 90 W; Ellman International Inc., NY, USA). In Pakistan, by the final 180-day evaluation, 83% of the patients had been cured (Shah *et al*. 2014). The efficacy of thermotherapy for CL caused by *L. panamensis* and *L. braziliensis* in Colombia was 64% for protocol and 58% for intention-to-treat, with odds of recurrence of 4·1% (López *et al*. 2012, 2013).

Adverse effects reported for thermotherapy were hyperpigmentation, secondary infections and satellite lesions (Asilian and Davami, 2006; Sadeghian *et al*. 2007; Bumb *et al*. 2013). Pain at the lesion site was also reported (López *et al*. 2012, 2013).

Cardona-Arias *et al*. (2015) stated that the efficacy of thermotherapy is statistically similar to that of systemic treatment. Thermotherapy is safer, requires fewer treatments and no laboratory monitoring, improves patient adherence and is less costly, and should be the first treatment option for CL in areas where the prevalence of the mucocutaneous form is low and in patients with contraindications for systemic treatment.

Thermotherapy is effective, relatively safe and caused acceptable superficial or minimal scarring. Its indication depends on the location and size/number of lesions. The method is suitable for areas with rudimentary medical infrastructure; occasionally it is applied in a single session, and is more effective than other methods. The rates of clinically cured patients show interpolated results (69·4–98·0%) between the two types of equipment used for RF therapy in thermotherapy. However, further studies to determine the factors that predispose patients to satellite lesions would be of value to increase overall safety and possibly develop thermotherapy into a first-line treatment for CL.

Cryotherapy

For CL caused by *L. tropica* in Iran, although the cryotherapy group showed a good response, the therapeutic failure rates were significantly higher than in the intralesional MA group (Layegh *et al*. 2009). Cryotherapy alone (57%) was as effective as intralesional MA (55%), and cryotherapy plus intralesional MA was the most effective treatment (90%); none of the cured lesions recurred during the follow-up period in Iran (Asilian *et al*. 2004*a*). For CL caused by *L. major*, 84% of the lesions were cured after 1–4 sessions of cryotherapy, with no recurrence, but the size and location of the lesions affected the clinical response (better results were obtained with lesions <1 cm and on the head) (Mosleh *et al*. 2008). Cryotherapy acts by destroying infected tissue and is best suited for single lesions (González *et al*. 2008).

Reported adverse effects of cryotherapy were erythema and oedema at the site, and hypo- or hyperpigmentation (Asilian *et al*. 2004*a*; Layegh *et al*. 2009). Burning and secondary infections were also reported (Mosleh *et al*. 2008).

Cryotherapy is effective, particularly when combined with MA, and offers the advantage of a small number of sessions, reducing the treatment time.

CO_2 laser

The CO_2 laser acts by specific thermolysis of infected tissue, with minor side-effects in normal tissue allowing collagen synthesis and remodelling (Walia and Alster, 1999; González *et al*. 2008). In Iran, the CO_2 laser was more effective than MA (93·7 *vs* 83·8%) (Asilian *et al*. 2004*b*). Over 93% complete response and no recurrence of CL were also described in Iran (Shamsi Meymandi *et al*. 2011). In Cuba, ten patients were treated with a single session, and all lesions were cured, with no relapses over a 2-year follow-up period (Rodríguez *et al*. 1990).

The most common adverse effects in CO_2 laser treatment were hyperpigmentation, persistent redness and hypertrophic scarring (Asilian *et al*. 2004*b*; Shamsi Meymandi *et al*. 2011).

Asilian *et al*. (2004*b*) stated that CL can be treated with CO_2 laser in a single session, which is more cost-effective than systemic antimony. CO_2 laser is effective within a few sessions, with relatively mild side-effects, and more studies are needed to determine the efficacy for the various *Leishmania* species.

Photodynamic therapy

PDT utilizes reactive oxygen species produced by a photosensitizer molecule in the presence of low-intensity visible light, to kill mammalian or microbial cells (Kharkwal *et al*. 2011). The clinical efficacy of PDT using 10% 5-aminolevulinic acid hydrochloride plus visible red light (633 nm) (ALA–PDT) was evaluated in patients with CL caused by *L. major* in Iran. The complete cure rate (lesions without amastigotes after 28 days) was 93·5% (Asilian and Davami, 2006).

An overall cure rate of 89% for CL caused by *L. major* and *L. tropica* (Enk *et al*. 2015) was obtained with daylight-activated PDT. Kharkwal *et al*. (2011) reported that *L. tropica* infection resistant to various therapeutic regimes was effectively treated with PDT. Based on a review of six papers, van der Snoek *et al*. (2008) suggested that PDT with porphyrin precursors is relatively effective in treating CL.

With ALA–PDT, adverse effects included pruritus, burning, redness, discharge, oedema and pain (Asilian and Davami, 2006). Hypo- or hyperpigmentation were also reported (van der Snoek *et al*. 2008).

Although only one study was evaluated here, ALA–PDT is a promising treatment for CL. A disadvantage of PDT is that it requires trained personnel and specific equipment. Its efficacy for other *Leishmania* species remains to be demonstrated.

CONCLUSION: EVIDENCE COMPARISON

Relevant review published on interventions for Old World cutaneous leishmaniasis (OWCL), revealed that there are no randomized clinical trials evidence that antimonials, intralesional or systemic, are of benefit in treating OWCL. Few treatments for CL have been well evaluated in randomized clinical trials [randomized controlled trials (RCTs)]. The inclusion criteria of this research were to evaluate the RCTs on treatments in immune-competent people with OWCL confirmed by smear, histology, culture or polymerase chain reaction (González *et al*. 2008). In our systematic review, the criteria were publications that describe topical treatment for CL, independently of the clinical stage of the disease.

González *et al*. (2008) reported that RCT review findings provided only reasonable evidence of benefit for 15% of topical PR + 12% of MBCL twice daily for 28 days or PDT weekly for 4 weeks in *L. major* infections. In addition, there was reasonable RCT PDT weekly for 4 weeks was more efficacious than topical 15% PR + 12% MBCL twice daily for 28 days. There was reasonable RCT evidence in *L. tropica* physical therapies such as CO_2 laser and cryotherapy. The findings of our systematic review provide strong evidence that the new treatments thermotherapy, PR and combinations, CO_2 laser, ALA–PDT, showed high cure rates with few adverse effects, relapses or recurrences, while cryotherapy showed a moderate cure rate. More studies are needed, with different species of *Leishmania* in different regions, to assess the overall effectiveness and safety of these treatments.

STRENGTHS AND LIMITATIONS OF THE STUDY

The accuracy of the search for the publications was guaranteed by the databases, the MeSH Terms and the repeated searches and analysis by consensus. The findings of the papers were organized and detailed in numerous tables, ensuring a good and faithful presentation of the data.

The lack of comparability of methods, including cure rates, follow-up periods, drug concentrations, *Leishmania* species treated, or the individual host response makes it almost impossible to compare the results of different studies. Creating multiple research centres, and sharing and comparing drugs and treatment methods are important to improve the results, side-effects and cure rates. Scientific publications have described and discussed the limitations of the studies, but this important information is not commonly available. Of the eight studies reviewed here, only three discussed their limitations.

SUPPLEMENTARY MATERIAL

The supplementary material for this article can be found at https://doi.org/10.1017/S0031182017000385.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Dr Diane McMahon-Pratt of Yale University for her valuable suggestions and careful analysis of the manuscript.

FINANCIAL SUPPORT

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

CONFLICTS OF INTEREST

None.

REFERENCES

Alavi-Naini, R, Fazaeli, A. and O'Dempsey, T. (2012). Topical treatment modalities for old world cutaneous leishmaniasis: a review. *Prague Medical Report* **113**, 105–118.

Alster, T. S. and Tanzi, E. (2004). Improvement of neck and cheek laxity with a nonablative radiofrequency device: a lifting experience. *Dermatologic Surgery* **30**, 503–507.

Arana, B. A., Mendoza, C. E., Rizzo, N. R. and Kroeger, A. (2001). Randomized, controlled, double-blind trial of topical treatment of cutaneous leishmaniasis with paromomycin plus methylbenzethonium chloride ointment in Guatemala. *American Journal of Tropical Medicine and Hygiene* **65**, 466–470.

Armijos, R. X., Weigel, M. M., Calvopiña, M., Mancheno, M. and Rodriguez, R. (2004). Comparison of the effectiveness of two topical paromomycin treatments versus meglumine antimoniate for New World cutaneous leishmaniasis. *Acta Tropica* **91**, 153–160.

Asilian, A. and Davami, M. (2006). Comparison between the efficacy of photodynamic therapy and topical paromomycin in the treatment of Old World cutaneous leishmaniasis: a placebo-controlled, randomized clinical trial. *Clinical and Experimental Dermatology* **31**, 634–637.

Asilian, A., Sadeghinia, A., Faghihi, G. and Momeni, A. (2004*a*). Comparative study of the efficacy of combined cryotherapy and intralesional meglumine antimoniate (Glucantime) vs. cryotherapy and intralesional meglumine antimoniate (Glucantime) alone for the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* **43**, 281–283.

Asilian, A., Sharif, A., Faghihi, G., Enshaeieh, S., Shariati, F. and Siadat, A. H. (2004*b*). Evaluation of CO_2 laser efficacy in the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* **43**, 736–738.

Ben Salah, A., Ben Messaoud, N., Guedri, E., Zaatour, A., Ben Alaya, N., Bettaieb, J., Gharbi, A., Belhadj Hamida, N., Boukthir, A., Chlif, S., Abdelhamid, K., El Ahmadi, Z., Louzir, H., Mokni, M., Morizot, G., Buffet, P., Smith, P. L., Kopydlowski, K. M., Kreishman-Deitrick, M., Smith, K. S., Nielsen, C. J., Ullman, D. R., Norwood, J. A., Thorne, G. D., McCarthy, W. F., Adams, R. C., Rice, R. M., Tang, D., Berman, J., Ransom, J., Magill, A. J. and Grogl, M. (2013). Topical paromomycin with or without gentamicin for cutaneous leishmaniasis. *New England Journal of Medicine* **368**, 524–532.

Bumb, R. A., Prasad, N., Khandelwal, K., Aara, N., Mehta, R. D., Ghiya, B. C., Salotra, P., Wei, L., Peters, S. and Satoskar, A. R. (2013). Long-term efficacy of single-dose radiofrequency-induced heat therapy vs. intralesional antimonials for cutaneous leishmaniasis in India. *British Journal of Dermatology* **168**, 1114–1119.

Cardona-Arias, J. A., Vélez, I. D. and López-Carvajal, L. (2015). Efficacy of thermotherapy to treat cutaneous leishmaniasis: a meta-analysis of controlled clinical trials. *PLoS ONE* **10**, e0122569.

Cota, G. F., de Sousa, M. R., Fereguetti, T. O., Saleme, P. S., Alvarisa, T. K. and Rabello, A. (2016). The cure rate after placebo or no therapy in american cutaneous leishmaniasis: a systematic review and meta-analysis. *PLoS ONE* **11**, e0149697.

Dorlo, T. P., Balasegaram, M., Beijnen, J. H. and de Vries, P. J. (2012). Miltefosine: a review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis. *Journal of Antimicrobial Chemotherapy* **67**, 2576–2597.

El-On, J., Jacobs, G. P., Witztum, E. and Greenblatt, C. L. (1984). Development of topical treatment for cutaneous leishmaniasis caused by *Leishmania major* in experimental animals. *Antimicrobial Agents and Chemotherapy* **26**, 745–751.

Enk, C. D., Nasereddin, A., Alper, R., Dan-Goor, M., Jaffe, C. L. and Wulf, H. C. (2015). Cutaneous leishmaniasis responds to daylight-activated photodynamic therapy: proof of concept for a novel self-administered therapeutic modality. *British Journal of Dermatology* **172**, 1364–1370.

Fernández, M. M., Malchiodi, E. L. and Algranati, I. D. (2011). Differential effects of paromomycin on ribosomes of *Leishmania mexicana* and mammalian cells. *Antimicrobial Agents and Chemotherapy* **55**, 86–93.

González, U., Pinart, M., Reveiz, L. and Alvar, J. (2008). Interventions for Old World cutaneous *leishmaniasis*. *Cochrane Database of Systematic Reviews* **8**.

Kharkwal, G. B., Sharma, S. K., Huang, Y. Y., Dai, T. and Hamblin, M. R. (2011). Photodynamic therapy for infections: clinical applications. *Lasers in Surgery and Medicine* **43**, 755–767.

Layegh, P., Pezeshkpoor, F., Soruri, A. H., Naviafar, P. and Moghiman, T. (2009). Efficacy of cryotherapy versus intralesional meglumine antimoniate (glucantime) for treatment of cutaneous leishmaniasis in children. *American Journal of Tropical Medicine and Hygiene* **80**, 172–175.

López, L., Robayo, M., Vargas, M. and Vélez, I. D. (2012). Thermotherapy. An alternative for the treatment of American cutaneous leishmaniasis. *Trials* **13**, 58.

López, L., Cruz, C., Godoy, G., Robledo, S. M. and Vélez, I. D. (2013). Thermotherapy effective and safer than miltefosine in the treatment of cutaneous leishmaniasis in Colombia. *The Revista do Instituto de Medicina Tropical de São Paulo* **55**.

Miranda-Verastegui, C., Llanos-Cuentas, A., Arevalo, I., Ward, B. J. and Matlashewski, G. (2005). Randomized, double-blind clinical trial of topical imiquimod 5% with parenteral meglumine antimoniate in the treatment of cutaneous leishmaniasis in Peru. *Clinical Infectious Diseases* **40**, 1395–1403.

Miranda-Verastegui, C., Tulliano, G., Gyorkos, T. W., Calderon, W., Rahme, E., Ward, B., Cruz, M., Llanos-Cuentas, A. and Matlashewski, G. (2009). First-line therapy for human cutaneous leishmaniasis in Peru using the TLR7 agonist imiquimod in combination with pentavalent antimony. *PLoS Neglected Tropical Diseases* **3**, e491.

Mosleh, I. M., Geith, E., Natsheh, L., Schonian, G., Abotteen, N. and Kharabsheh, S. (2008). Efficacy of a weekly cryotherapy regimen to treat *Leishmania major* cutaneous leishmaniasis. *Journal of the American Academy of Dermatology* **58**, 617–624.

Motta, J. O. and Sampaio, R. N. (2012). A pilot study comparing low-dose liposomal amphotericin B with N-methyl glucamine for the treatment of American cutaneous leishmaniasis. *Journal of the European Academy of Dermatology and Venereology* **26**, 331–335.

Munir, A., Janjua, S. A. and Hussain, I. (2008). Clinical efficacy of intramuscular meglumine antimoniate alone and in combination with intralesional meglumine antimoniate in the treatment of Old World cutaneous leishmaniasis. *Acta Dermatovenerologica Croatica* **16**, 60–64.

Nascimento, E., Fernandes, D. F., Vieira, E. P., Campos-Neto, A., Ashman, J. A., Alves, F. P., Coler, R. N., Bogatzki, L. Y., Kahn, S. J., Beckmann, A. M., Pine, S. O., Cowgill, K. D., Reed, S. G. and Piazza, F. M. (2010). A clinical trial to evaluate the safety and immunogenicity of the LEISH-F1+MPL-SE vaccine when used in combination with meglumine antimoniate for the treatment of cutaneous leishmaniasis. *Vaccine* **28**, 6581–6587.

Neves, L. O., Talhari, A. C., Gadelha, E. P., Silva Júnior, R. M., Guerra, J. A., Ferreira, L. C. and Talhari, S. (2011). A randomized clinical trial comparing meglumine antimoniate, pentamidine and amphotericin B for the treatment of cutaneous leishmaniasis by *Leishmania guyanensis*. *Anais Brasileiros de Dermatologia* **86**, 1092–1101.

Nilforoushzadeh, M. A., Jaffary, F., Ansari, N., Siadat, A. H., Nilforoushan, Z. and Firouz, A. (2008). A comparative study between the efficacy of systemic meglumine antimoniate therapy with standard or low dose plus oral omeprazole in the treatment of cutaneous leishmaniasis. *Journal of Vector Borne Diseases* **45**, 287–291.

Reithinger, R., Mohsen, M., Wahid, M., Bismullah, M., Quinnell, R. J., Davies, C. R., Kolaczinski, J. and David, J. R. (2005). Efficacy of thermotherapy to treat cutaneous leishmaniasis caused by *Leishmania tropica* in Kabul, Afghanistan: a randomized, controlled trial. *Clinical Infectious Diseases* **40**, 1148–1155.

Rodríguez, M. E., Inguanzo, P., Ramos, A. and Pérez, J. (1990). Treatment of cutaneous leishmaniasis with CO_2 laser radiation. *Revista Cubana de Medicina Tropical* **42**, 197–202.

Sadeghian, G. and Nilforoushzadeh, M. A. (2006). Effect of combination therapy with systemic glucantime and pentoxifylline in the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* **45**, 819–821.

Sadeghian, G., Nilfroushzadeh, M. A. and Iraji, F. (2007). Efficacy of local heat therapy by radiofrequency in the treatment of cutaneous leishmaniasis, compared with intralesional injection of meglumine antimoniate. *Clinical and Experimental Dermatology* **32**, 371–374.

Safi, N., Davis, G. D., Nadir, M., Hamid, H., Robert, L. L., Jr. and Case, A. J. (2012). Evaluation of thermotherapy for the treatment of cutaneous leishmaniasis in Kabul, Afghanistan: a randomized controlled trial. *Military Medicine* **177**, 345–351.

Santos, J. B., de Jesus, A. R., Machado, P. R., Magalhaes, A., Salgado, K., Carvalho, E. M. and Almeida, R. P. (2004). Antimony plus recombinant human granulocyte-macrophage colony-stimulating factor applied topically in low doses enhances healing of cutaneous Leishmaniasis ulcers: a randomized, double-blind, placebo-controlled study. *Journal of Infectious Diseases* **190**, 1793–1796.

Shah, S. A., Memon, A. A., Auwj-e-Shamim, Baqi, S. and Witzig, R. (2014). Low-cost thermotherapy for cutaneous leishmaniasis in Sindh, Pakistan. *JPMA. The Journal of the Pakistan Medical Association* **64**, 1398–1404.

Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P. and Stewart, L. A. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* **349**, g7647.

Shamsi Meymandi, S., Zandi, S., Aghaie, H. and Heshmatkhah, A. (2011). Efficacy of CO_2 laser for treatment of anthroponotic cutaneous leishmaniasis, compared with combination of cryotherapy and intralesional meglumine antimoniate. *Journal of the European Academy of Dermatology and Venereology* **25**, 587–591.

Solomon, M., Baum, S., Barzilai, A., Scope, A., Trau, H. and Schwartz, E. (2007). Liposomal amphotericin B in comparison to sodium stibogluconate for cutaneous infection due to *Leishmania braziliensis*. *Journal of the American Academy of Dermatology* **56**, 612–616.

Solomon, M., Pavlotzky, F., Barzilai, A. and Schwartz, E. (2013). Liposomal amphotericin B in comparison to sodium stibogluconate for *Leishmania braziliensis* cutaneous leishmaniasis in travelers. *Journal of the American Academy of Dermatology* **68**, 284–289.

Sosa, N., Capitan, Z., Nieto, J., Nieto, M., Calzada, J., Paz, H., Spadafora, C., Kreishman-Deitrick, M., Kopydlowski, K., Ullman, D., McCarthy, W. F., Ransom, J., Berman, J., Scott, C. and Grogl, M. (2013). Randomized, double-blinded, phase 2 trial of WR 279,396 (paromomycin and gentamicin) for cutaneous leishmaniasis in Panama. *American Journal of Tropical Medicine and Hygiene* **89**, 557–563.

Soto, J. M., Toledo, J. T., Gutierrez, P., Arboleda, M., Nicholls, R. S., Padilla, J. R., Berman, J. D., English, C. K. and Grogl, M. (2002). Treatment of cutaneous leishmaniasis with a topical antileishmanial drug (WR279396): phase 2 pilot study. *American Journal of Tropical Medicine and Hygiene* **66**, 147–151.

Trinconi, C. T., Reimão, J. Q., Yokoyama-Yasunaka, J. K., Miguel, D. C. and Uliana, S. R. (2014). Combination therapy with tamoxifen and amphotericin B in experimental cutaneous leishmaniasis. *Antimicrobial Agents and Chemotherapy* **58**, 2608–2613.

van der Snoek, E. M., Robinson, D. J., van Hellemond, J. J. and Neumann, H. A. (2008). A review of photodynamic therapy in cutaneous leishmaniasis. *Journal of the European Academy of Dermatology and Venereology* **22**, 918–922.

Walia, S. and Alster, T. S. (1999). Prolonged clinical and histologic effects from CO2 laser resurfacing of atrophic acne scars. *Dermatologic Surgery* **25**, 926–930.

World Health Organization (2010). Technical Report Series 949 – Control of Leishmaniasis. http://apps.who.int/iris/bitstream/10665/44412/1/WHO_TRS_949_eng.pdf.

World Health Organization (2016). Leishmaniasis. Fact sheet. Updated March 2016. http://www.who.int/mediacentre/factsheets/fs375/en/.