REVIEW ARTICLE

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

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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)

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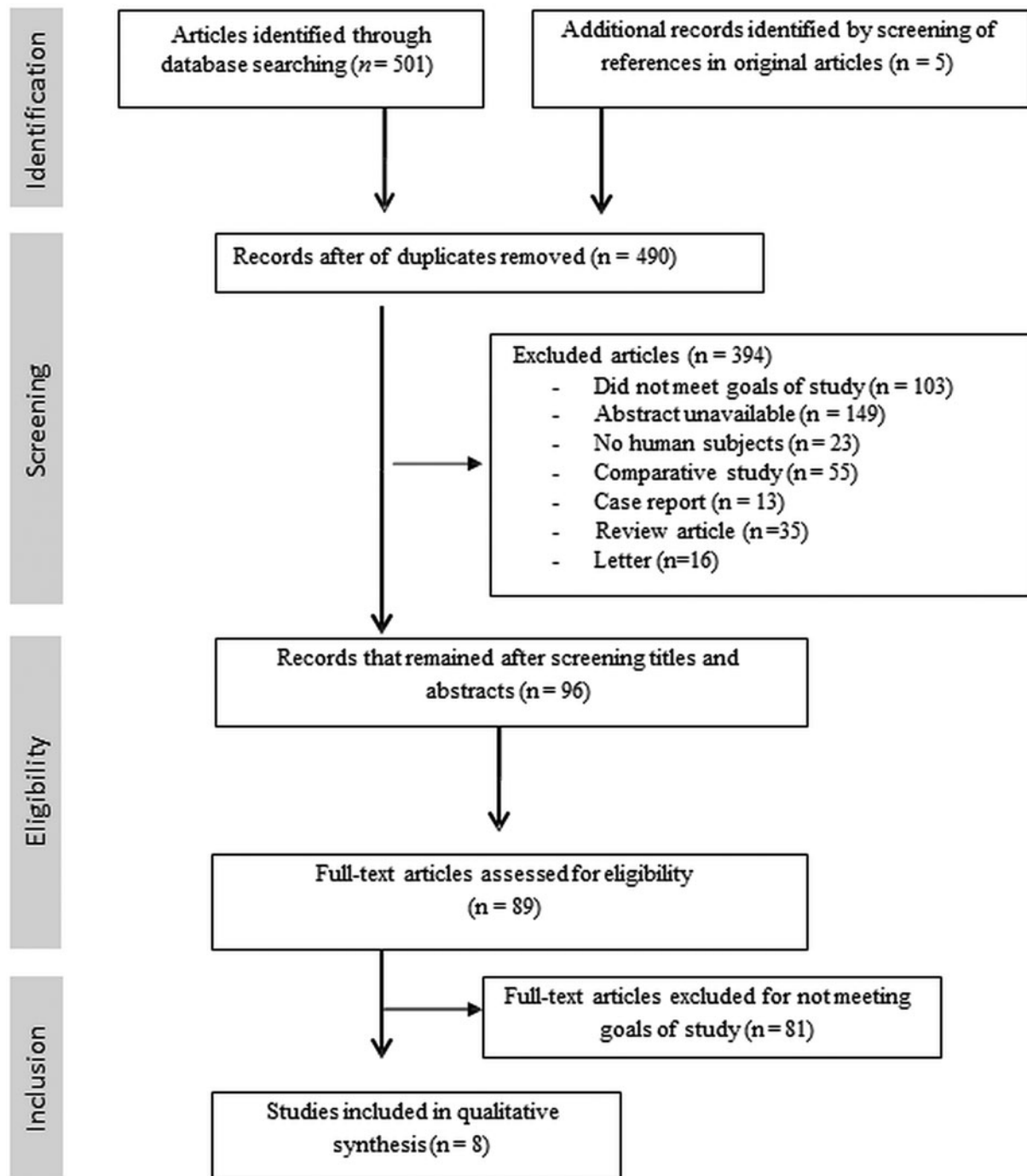
Fig. 1. Flow diagram of study selection for the systematic review.

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. (2004a, 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. 2004b; 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. 2004b; 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. 2004b) and three after 6 months (Asilian et al. 2004b; 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. 2004b; 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. 2004b; 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. 2004b; 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. 2004b).

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. (2004a, 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. (2004a, 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. (2004a, 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.

CONFLICTS OF INTEREST

None.

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