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Systematic Review

Eligibility criteria and outcome measures adopted in clinical trials of treatments of cutaneous leishmaniasis: systematic literature review covering the period 1991–2015

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Abstract

OBJECTIVE To document the sources of heterogeneity in outcomes and shortcomings in trial designs reported by previous systematic reviews.

METHODS Systematic review of clinical trials of CL treatments published since 1991, to assess and compare eligibility criteria and outcome measures in trials (any type of treatment) of CL (any form) reported before and after the publication of the CONSORT statement.

RESULTS We identified 106 eligible trials published between 1991 and 2015, 74% after the 2001 CONSORT statement; 58% (n = 63) were on Old-World CL and 37% (n = 40) in New-World CL; overall, 11 531 patients enrolled in 243 treatment groups on 30 different treatments. Both requirements and definitions for eligibility and outcome criteria varied. Compliance with CONSORT requirements increased for studies published after the 2010 update. As for entry criteria, 94% of studies had a requirement for sex (74% of those enrolling also women excluded those who were pregnant or lactating), 69% for age (variable age ranges), 99% parasitological confirmation, 43% prior duration of illness (14% excluded cases with previous episodes), 46% defined the number, 28% the size and 13% the type of lesions (27% with restrictions as to their anatomical location). Follow-up ranged 1–24 months, with 14% and 91% of studies, respectively, having defined initial and final cure.

CONCLUSIONS This review documents changes in reporting before and after the publication of the CONSORT statement. Lack of standardisation, compounded with the small number of trials relative to the magnitude of the disease in its multiple forms, and with the range of treatments tested explains why evidence to inform treatment guidelines is generally weak for CL. Adopting standardised methodologies will improve the quality and consistency of clinical trials, and ultimately yield better treatments for CL.

keywords cutaneous leishmaniasis, systematic review, eligibility criteria, outcome measures

Introduction

The leishmaniases are diseases caused by parasites belonging to the genus *Leishmania* transmitted to humans through the bite of sand flies: *Lutzomyia* (New World) and *Phlebotomus* (Old World) [1]. They are present in 98 countries and cause some 900 000 to 1.3 million cases annually [2, 3]. Of the three clinical manifestations (visceral, mucocutaneous, cutaneous), the latter, cutaneous leishmaniasis (CL), is the most prevalent, contributing circa 90% of all cases [3–5]. Clinical manifestations of CL, which include most commonly ulcers, nodules and papules, depend on the causative parasite species: *L. braziliensis, L. peruviana, L. guyanensis, L. panamensis, L. amazonensis* and *L. mexicana* in the Americas (New-World CL, NWCL), and *L. major, L. tropica* and *L. aethiopica* in Asia, Africa and Europe (Old-World CL, OWCL) [4, 6].

Like other neglected tropical diseases (NTD), case management is a problem in CL, largely because little, if any, drug research and development (R&D) is conducted on this disease of no commercial interest [7–10]. This translates into a miscellaneous therapeutic armamentarium ranging from systemic treatments with pentavalent

antimonials, pentamidine, miltefosine, amphotericin B, to local treatments using physical therapy or direct application of medications with some level of activity on the parasites in various pharmaceutical preparations [6, 8, 11]. With very few exceptions, these treatments are more the result of empirical use of existing medications than a planned R&D effort for CL and are often ill-adapted and inconvenient, and some carry significant safety liabilities. Furthermore, the effects of most of these treatments are inconsistently assessed and reported [7–12], which means that treatment guidelines are based on weak evidence [1].

To address these fundamental issues of heterogeneity, design and conduct of treatment trials for CL [8, 13], which are hampering consistent and effective case management, a guidance document was prepared. Its aim is to provide clinical investigators with guidance for the design, conduct, analysis and report of clinical trials of treatments for CL, while recognising the complexity of the disease, and to enhance the capacity for high-quality trials meeting the requirements of Good Clinical Practice standards [14]. Standardising methods is important to allow between-study comparability and informative meta-analysis, to strengthen the evidence for recommendations on treatment and case management, and ultimately to improve CL case management and control. Inadequate trials may lead to inappropriate conclusions and are an unethical and inefficient use of the limited resources available for neglected diseases such as CL. Consolidating the guidelines to design and conduct of clinical trials for CL will have a positive impact on comparability, interpretation and validity of findings derived of treatment researches, allowing evidence-based decisions and directing patients according to their risk and characteristics. This effort should also be seen in the context of more general ongoing initiatives to improve the quality of reporting of clinical trials Consolidated Standards of Reporting Trials statement (CONSORT) [15–17].

Important elements that might account for the apparent heterogeneity of clinical trial outcomes are the characteristics of the treated populations and how treatment effects are measured. We therefore conducted a systematic review of the eligibility criteria and outcome measures adopted in treatment trials of CL conducted during 1991–2015.

Methods

Given that the aim of this systematic review was not to evaluate the efficacy of a specific intervention, the research question was defined in terms of eligibility criteria and cure measures; thus, 'in patients diagnosed with CL (any form) and enrolled in treatment trials (any type of treatment), how do eligibility criteria and outcome measures compare across studies?'

Eligibility

Inclusion criteria were as follows: (i) studies that include the search terms in title and/or abstract; (ii) clinical trials (all study designs allowed); (iii) original studies investigating the efficacy and safety of treatments (all treatments and routes of administration allowed) of CL (all forms). The search was not restricted by time or language.

We excluded systematic reviews, descriptive studies and analytic studies that only evaluated one group of treatment, trials on clinical manifestations different from CL or complications thereof, co-infection with HIV, and papers reporting insufficient details on methods or papers that were not available in full.

Study identification

The following databases were interrogated: PubMed, OVID, ScienceDirect, EMBASE, Wiley, Web of Science, Scielo, Lilacs, ACP Journal Club, DARE, Springer Link, Jama Network, Oxford Journals and Cochrane. Limited to title and abstract, the following terms were used for the search: 'cutaneous leishmaniasis' in combination with 'treatment', 'topical treatment', 'local treatment', 'local heat', 'heat therapy', 'systemic treatment', 'combined treatment', 'antimonials', 'azoles', 'antibiotic', 'antiprotozoal', 'antifungal', 'antineoplastic'. Papers identified through the combined strategies were exported to EndNote Web.

Using the advanced search option available in the different databases, examples of the syntax used are as follows: (cutaneous leishmaniasis[Title/Abstract]) AND treatment[Title/Abstract]; (ti:(cutaneous leishmaniasis)) AND (ti:(treatment)); ((ab:(cutaneous leishmaniasis))) AND (ab:(treatment)); (tw:(cutaneous leishmaniasis)) AND (tw:(treatment)); TITLE-ABSTR-KEY(cutaneous leishmaniasis) and TITLE-ABSTR-KEY(treatment).

Study selection

After screening out duplicate references, we reviewed all remaining papers in English, Spanish and Portuguese. From the studies meeting the inclusion criteria (see above), two investigators independently extracted and recorded in a specially designed Excel form the study variables (year, language, type of CL, country, clinical phase, randomised, type and number of study arms, sex, age, diagnosis method, specie identification, time of evolution, size, type and number of lesions, anatomical location, pregnant, lactating or childbearing-age women, previous history of CL, previous treatment, laboratory test, electrocardiogram, follow-up time, outcome definitions). To guarantee reproducibility of the data

collection, every investigator filled the forms separately. Discrepancies were resolved by consensus or by involving a third person. For papers whose full text was not available, we emailed authors to request it.

Statistical analysis

We report absolute and relative frequencies of the variables of interest by year of publication using 2001 (when the CONSORT guideline was published for the first time).

Results

Description of clinical trials

We identified 75 875 papers published between 1991 and 2015, which became 2238 after removing duplicate articles and 106 after applying the eligibility criteria (Figure 1).

English was the predominant language (94%, n = 102). As to the geographical localisation, 58% (n = 63) were on OWCL and 37% (n = 40) in NWCL; Iran, Brazil and Colombia were the most represented countries, contributing 33% (n = 36), 14% (n = 15) and 13% (n = 14) of studies, respectively; 85% (n = 92) of studies did not report the clinical phase of the investigation (Table 1 and Figure 2).

Overall, these studies enrolled 11 531 patients in 243 treatment groups; 88% (n = 95) of studies were randomised; 82 had two arms (n = 8115), 17 had three arms (n = 2763), and seven had four arms (n = 653). They enrolled a median 80 patients (range 10–444) per study; the breakdown by number of arms was 76 (range 10–382) for two-arm studies, 124 (range 20–444) for three-arm studies and 92 (range 62–150) for four-arm studies.

Systemic treatment (oral, intramuscular or intravenous) was administered in 47.3% (n = 115) of treatment groups (5174 patients (44.9%)), and local treatment was

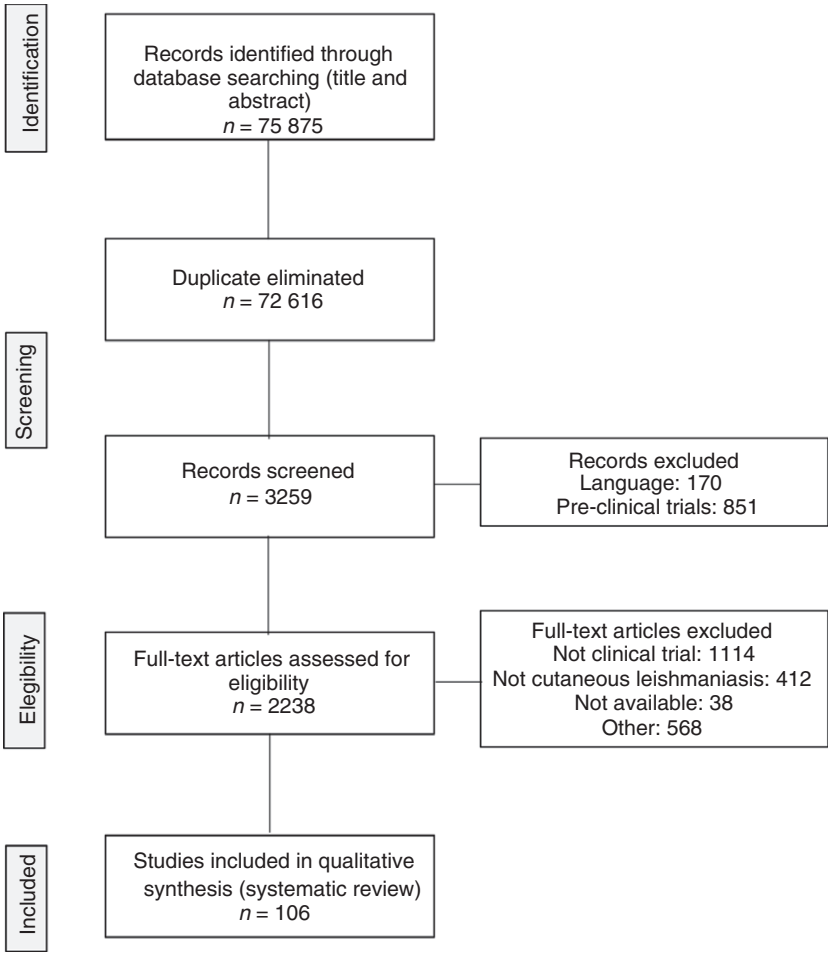

Figure 1 Article selection algorithm.

Table 1 Main characteristics of studies included in this review

CONSORT	Ref.	Author	Year	Language	Type of CL	Country	Clinical phase	Randomised	Type and number of study arms			
									1 *n*	2 *n*	3 *n*	4 *n*
Before statement	[110]	Dogra *et al.*	1991	English	OWCL	India	Not reported	Yes	Or 60	Or (P) 60	–	–
2001	[18]	Lynen *et al.*	1992	English	OWCL	Sudan	Not reported	Yes	Top 33	Top 33	–	–
	[108]	Martínez *et al.*	1992	English	NWCL	Colombia	Not reported	Yes	IM 33	IM + Or 35	Or 25	NT 17
	[112]	Soto *et al.*	1993	English	NWCL	Colombia	Not reported	No	IM 23	IM 27	Or 20	NT 22
	[19]	Alsaleh *et al.*	1995	English	OWCL	Kuwait	Not reported	Yes	Or 18	Or 15	–	–
	[22]	Asilian *et al.*	1995	English	OWCL	Iran	Not reported	Yes	Top 126	Top (P) 125	–	–
	[23]	Ben *et al.*	1995	English	OWCL	Tunisia	Not reported	Yes	Top 57	Top (P) 58	–	–
	[26]	Correira *et al.*	1996	Portuguese	NWCL	Brazil	Not reported	Yes	IM 15	IM 15	IM 16	IM 16
	[27]	Dogra *et al.*	1996	English	OWCL	India	Not reported	Yes	Or 10	Or 10	–	–
	[109]	Martínez *et al.*	1996	English	NWCL	Colombia	Not reported	Yes	IM 49	IM + Or 51	–	–
	[100]	Alkhawajah *et al.*	1997	English	OWCL	Saudi Arabia	Not reported	Yes	IM 31	IL 36	–	–
	[28]	D'Oliveira *et al.*	1997	English	NWCL	Brazil	Not reported	Yes	Or 18	IV 16	–	–
	[29]	Ozgoztasi *et al.*	1997	English	OWCL	Turkey	Not reported	Yes	Top 40	Or 32	–	–
	[30]	Sharquie *et al.*	1997	English	OWCL	Iraq	Not reported	Yes	IL 19	IL 17	IL 18	NT 9
	[31]	Vélez *et al.*	1997	English	NWCL	Colombia	III	Yes	Or 60	Or (P) 56	IM 66	–
	[32]	Hendrickx *et al.*	1998	English	NWCL	Colombia	Not reported	No	Or 15	Or (P) 56	IM 66	–
	[33]	Soto *et al.*	1998	English	NWCL	Colombia	III	Yes	Top + IM 59	Top (P) + IM 30	Top + IM 30	IM 31
	[34]	Almeida *et al.*	1999	English	NWCL	Brazil	Not reported	Yes	IV + IL 10	IV + IL (P) 10	–	–
	[101]	Saldanha *et al.*	1999	Portuguese	NWCL	Brazil	Not reported	No	IV o IM 58	IV o IM 69	–	–

Table I (*Continued*)

CONSORT	Ref.	Author	Year	Language	Type of CL	Country	Clinical phase	Randomised	Type and number of study arms			
									1 *n*	2 *n*	3 *n*	4 *n*
	[123]	Laguna-Torres *et al.*	1999	Portuguese	NWCL	Brazil	Not reported	Yes	Or 5	IV 5	–	–
	[35]	Mujtaba *et al.*	1999	English	OWCL	Pakistan	Not reported	Yes	IL 49	IL 47	–	–
	[36]	Deps *et al.*	2000	Portuguese	NWCL	Brazil	Not reported	No	IM 31	IM 32	–	–
	[118]	Kochar *et al.*	2000	English	OWCL	India	Not reported	Yes	Or 23	Or (P) 23	–	–
	[37]	Arana *et al.*	2001	English	NWCL	Guatemala	Not reported	Yes	Top 38	Top (P) 38	–	–
	[38]	Palacios *et al.*	2001	English	NWCL	Colombia	Not reported	Yes	IM 68	IM 68	–	–
	[39]	Salmanpour *et al.*	2001	English	OWCL	Iran	Not reported	Yes	Or 64	IL 32	–	–
	[40]	Sharquie *et al.*	2001	English	OWCL	Iraq	Not reported	Yes	Or 31	Or 29	Or 32	NT 12
	[111]	Soto *et al.*	2001	English	NWCL	Colombia	I/II	No	Or 16	Or 19	Or 17	Or 20
After statement 2001	[102]	Alrajh *et al.*	2002	English	OWCL	Saudi Arabia	Not reported	Yes	Or 106	Or (P) 103	–	–
	[121]	Esfandiarpour *et al.*	2002	English	OWCL	Iran	Not reported	Yes	Or 50	IM 50	Or + IM 50	–
	[41]	Momeni *et al.*	2002	English	OWCL	Iran	Not reported	Yes	ND 36	ND 36	–	–
	[113]	Soto *et al.*	2002	English	NWCL	Colombia	II	Yes	Top 33	Top (P) 12	–	–
	[42]	Wortmann *et al.*	2002	English	NWCL	USA	Not reported	Yes	IV 19	IV 19	–	–
	[21]	Asilian *et al.*	2003	English	OWCL	Iran	Not reported	Yes	Top 108	Top + Top (P) 108	–	–
	[43]	Ribiero de Paula *et al.*	2003	Portuguese	NWCL	Brazil	Not reported	No	IM 38	IV 41	–	–
	[44]	Armijos *et al.*	2004	English	NWCL	Ecuador	Not reported	Yes	Top 40	Top 40	IM 40	–
	[45]	Santos *et al.*	2004	English	NWCL	Brazil	Not reported	Yes	IV + IL 10	IV + IL (P) 10	–	–
	[46]	Firooz *et al.*	2005	English	OWCL	Iran	Not reported	Yes	IL 36	IL 36	–	–

Table 1 (*Continued*)

CONSORT	Ref.	Author	Year	Language	Type of CL	Country	Clinical phase	Randomised	Type and number of study arms			
									1 *n*	2 *n*	3 *n*	4 *n*
	[103]	Andersen *et al.*	2005	English	NWCL	Peru	Not reported	Yes	IV 40	IV 40	–	–
	[47]	Miranda *et al.*	2005	English	NWCL	Peru	Not reported	Yes	IV o IM + Top 20	IV o IM + Top 20	–	–
	[48]	Nassiri *et al.*	2005	English	OWCL	Iran	Not reported	Yes	Or 100	Or (P) 100	–	–
	[49]	Reithinger *et al.*	2005	English	OWCL	Afghanistan	Not reported	Yes	IL 148	IM 144	Loc 139	–
	[117]	Shazad *et al.*	2005	English	OWCL	Iran	Not reported	Yes	Top 30	IL 30	–	–
	[20]	Asilian *et al.*	2006	English	OWCL	Iran	Not reported	Yes	Loc 20	Top 20	Top (P) 20	–
	[104]	Firooz *et al.*	2006	English	OWCL	Iran	Not reported	Yes	Top + IM 59	Top (P) + IM 60	–	–
	[122]	Jaffar *et al.*	2006	English	OWCL	Saudi Arabia	Not reported	Yes	Or 46	Or (P) 16	–	–
	[50]	Kochar *et al.*	2006	English	OWCL	India	Not reported	Yes	Or 25	Or (P) 25	–	–
	[51]	Lobo *et al.*	2006	English	NWCL	Brazil	Not reported	Yes	Loc 17	IV 20	–	–
	[54]	Nilforoushzadeh *et al.*	2006	English	OWCL	Iran	Not reported	Yes	Top 40	IL 40	–	–
	[53]	Sadeghian *et al.*	2006	English	OWCL	Iran	Not reported	Yes	Or + IM 32	Or (P) + IM 31	–	–
	[55]	Arevalo *et al.*	2007	English	NWCL	Peru	Not reported	Yes	IV 7	Top 6	Top + IV 7	–
	[56]	Khan *et al.*	2007	English	OWCL	Pakistan	Not reported	Indeterminate	Or 15	IM 15	–	–
	[57]	Krolewiecki *et al.*	2007	English	NWCL	Argentina	Not reported	Yes	Or 22	IV 23	–	–
	[58]	Layegh *et al.*	2007	English	OWCL	Iran	Not reported	Yes	Or 22	IM 27	–	–
	[105]	Mohebali *et al.*	2007	English	OWCL	Iran	Not reported	Yes	Or 32	IM 31	–	–
	[106]	Nilforoushzadeh *et al.*	2007	English	OWCL	Iran	Not reported	Yes	IL + Top 45	IL 45	–	–

Table I (*Continued*)

CONSORT	Ref.	Author	Year	Language	Type of CL	Country	Clinical phase	Randomised	Type and number of study arms			
									1 *n*	2 *n*	3 *n*	4 *n*
	[59]	Rahman *et al.*	2007	English	OWCL	Pakistan	Not reported	No	Or 15	IM 15	–	–
	[60]	Sadeghian *et al.*	2007	English	OWCL	Iran	Not reported	Yes	Loc 57	IL 60	–	–
	[107]	Nilforoushzadeh *et al.*	2008	English	OWCL	Iran	Not reported	Yes	Or (P) + IM 43	Or + IM 36	Or (P) + IM 45	–
	[52]	Miranda *et al.*	2009	English	NWCL	Peru	Not reported	Yes	Top + IV 40	Top (P) + IV 40	–	–
	[25]	Ben *et al.*	2009	English	OWCL	Tunisia - France	II	Yes	Top 49	Top (P) 41	–	–
	[61]	Layegh *et al.*	2009	English	OWCL	Iran	Not reported	Yes	Loc 40	IL 39	–	–
	[62]	Aronson *et al.*	2010	English	OWCL	Iran	Not reported	Yes	Loc 28	IV 28	–	–
	[63]	Bumb *et al.*	2010	English	OWCL	India	Not reported	No	Loc 110	Loc 110	–	–
	[64]	El-Sayen *et al.*	2010	English	OWCL	Yemen	Not reported	Yes	IL 10	IL + IM 10	IL + Or 10	–
	[65]	Lopez *et al.*	2010	English	NWCL	Colombia	Not reported	Yes	Top + IM 88	Top (P) + IM 90	–	–
	[66]	Machado *et al.*	2010	English	NWCL	Brazil	Not reported	Yes	Or 60	IV 30	–	–
	[67]	Mapar *et al.*	2010	English	OWCL	Iran	Not reported	Yes	IL 18	IL 18	–	–
	[68]	Ranawaka *et al.*	2010	English	OWCL	Sri Lanka	Not reported	Yes	IL 87	IL 67	–	–
	[69]	Meymandi *et al.*	2010	English	OWCL	Iran	Not reported	Yes	Loc 96	Loc + IL 95	–	–
	[116]	Vélez *et al.*	2010	English	NWCL	Colombia	III	Yes	Or 145	IM 143	–	–
	[70]	Chrusciak-Talhari *et al.*	2011	English	NWCL	Brazil	II–III	Yes	Or 60	IV 30	–	–
	[71]	Emad *et al.*	2011	English	OWCL	Iran	Not reported	Yes	Or 60	Or 60	–	–
	[72]	Layegh *et al.*	2011	English	OWCL	Iran	Not reported	Yes	Top 50	IL 60	–	–

Table I (*Continued*)

CONSORT	Ref.	Author	Year	Language	Type of CL	Country	Clinical phase	Randomised	Type and number of study arms			
									1 *n*	2 *n*	3 *n*	4 *n*
	[73]	Neves *et al.*	2011	English	NWCL	Brazil	Not reported	Yes	IM o IV 74	IM 74	IV 37	–
	[74]	Meymandi *et al.*	2011	English	OWCL	Iran	Not reported	Yes	Loc + Top 39	IL 36	–	–
	[76]	Yazdanpanah *et al.*	2011	English	OWCL	Iran	Not reported	Yes	Or 26	IM 74	–	–
	[75]	Nilforoushzadeh *et al.*	2012	English	OWCL	Iran	Not reported	Yes	IL 30	Loc + Top 30	–	–
	[78]	Dastgheib *et al.*	2012	English	OWCL	Iran	Not reported	No	Or 36	IM 35	–	–
	[79]	Jowkar *et al.*	2012	English	OWCL	Iran	Not reported	Yes	Loc + Top 36	Loc + Top 27	–	–
	[115]	Lopez *et al.*	2012	English	NWCL	Colombia	III	Yes	Loc 149	IM 143	–	–
	[80]	Maleki *et al.*	2012	English	OWCL	Iran	Not reported	Yes	IL 24	IL 10	–	–
	[81]	Rubiano *et al.*	2012	English	NWCL	Colombia	Not reported	Yes	Or 58	IM 58	–	–
	[82]	Safi *et al.*	2012	English	OWCL	Afghanistan	Not reported	Yes	Loc 189	IL 193	–	–
	[77]	Bumb *et al.*	2013	English	OWCL	India	IV	Yes	Loc 50	IL 50	–	–
	[24]	Ben *et al.*	2013	English	OWCL	Tunisia	III	Yes	Top 125	Top 125	Top (P) 125	–
	[83]	Khatami *et al.*	2013	English	OWCL	Iran	Not reported	Yes	IL 26	IL + Top (P) 26	IL + Top 31	–
	[114]	Lopez *et al.*	2013	English	NWCL	Colombia	III	Yes	Loc 149	Or 145	–	–
	[84]	Sosa *et al.*	2013	English	NWCL	Panama	II	Yes	Top 15	Top 15	–	–
	[85]	Soto *et al.*	2013	English	NWCL	Bolivia	Not reported	Yes	IL 30	Loc 20	Top (P) 30	–
	[86]	Toledo *et al.*	2014	English	NWCL	Brazil	III	Yes	IM o IV 24	Or 24	–	–
	[87]	Ejaz *et al.*	2014	English	OWCL	Pakistan	Not reported	Yes	IM 151	IM + Or 173	–	–

Table I (*Continued*)

CONSORT	Ref.	Author	Year	Language	Type of CL	Country	Clinical phase	Randomised	Type and number of study arms			
									1 *n*	2 *n*	3 *n*	4 *n*
	[88]	Jaffary *et al.*	2014	English	OWCL	Iran	Not reported	Yes	Top 55	Top 55	IL 55	–
	[89]	Jaffary *et al.*	2014	English	OWCL	Iran	Not reported	Yes	IL + Top 30	IL + Top (P) 30	–	–
	[90]	Jebran *et al.*	2014	English	OWCL	Afghanistan	IIa	Yes	Loc + Top 73	Loc + Top 62	–	–
	[91]	Shanehsaz *et al.*	2014	English	OWCL	Syria	Not reported	Yes	IM 30	IM 30	–	–
	[119]	Stahl *et al.*	2014	English	OWCL	Afghanistan	IIb	Yes	IL 24	Loc 32	Loc 31	–
	[92]	Al-Sudany *et al.*	2015	English	OWCL	Iran	Not reported	No	Loc 25	NT	–	–
	[93]	Daie *et al.*	2015	English	OWCL	Iran	Not reported	Yes	Top 22	IL 25	–	–
	[94]	Farajzadeh *et al.*	2015	English	OWCL	Iran	Not reported	Yes	Or + Loc 40	IM 40	–	–
	[95]	Hu *et al.*	2015	English	NWCL	Suriname	Not reported	Yes	IM 84	IM 79	–	–
	[96]	Janghorbani *et al.*	2015	English	OWCL	Iran	Not reported	Yes	IM o IL 80	Top 80	–	–
	[97]	Ranawaka *et al.*	2015	English	OWCL	Sri Lanka	Not reported	Yes	IL 170	IL 192	IL 82	–
	[98]	Shanehsaz *et al.*	2015	English	OWCL	Syria	Not reported	Yes	IM + Or (P) 30	IM + Or 30	IM + Or (P) 30	–
	[120]	Sharquie *et al.*	2015	English	OWCL	Iraq	Not reported	No	Loc 35	NT	–	–
	[99]	Sharquie *et al.*	2015	English	OWCL	Iraq	Not reported	No	Top 65	NT	–	–

n, sample size; Top, Topic; IL, Intralesional; IM, intramuscular; IV, Intravenous; Or, Oral; NT, No treatment-: not applicable; (P), Placebo.

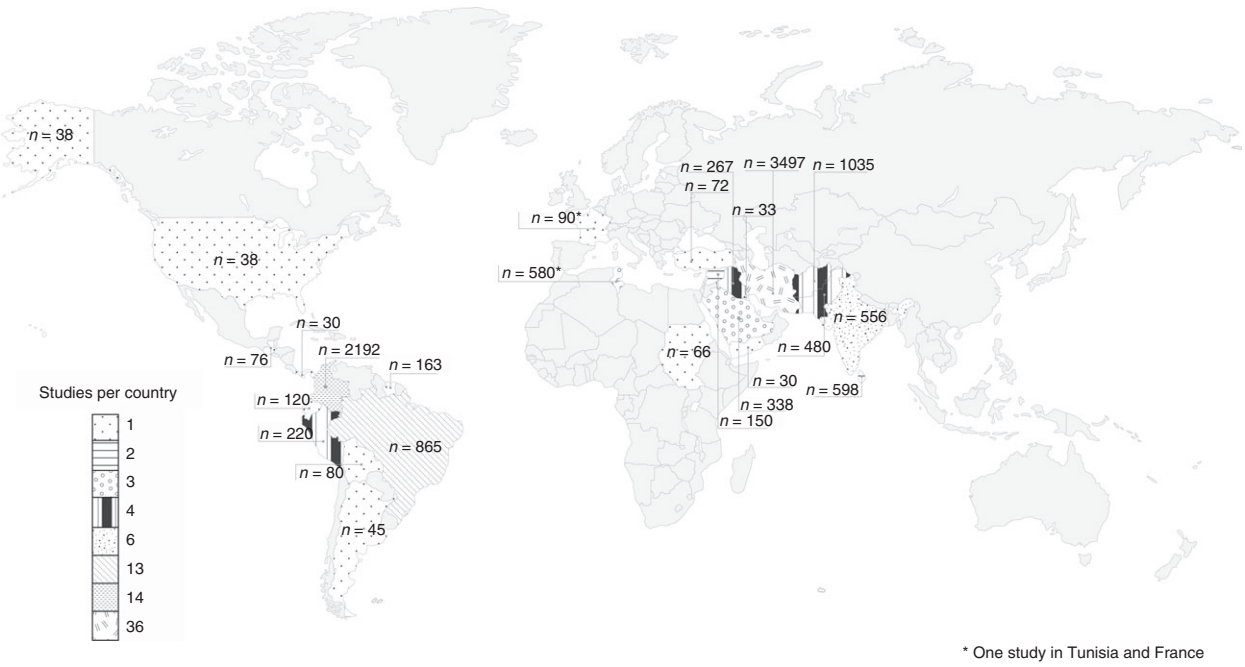

Figure 2 Geographical distribution of trials and patients enrolled.

given to 36.2% (n = 88; 5497 patients (47.8%)), consisting of: 22.2% (n = 54) local applications of heat or cold or intralesional injections, 14% (n = 34) topical treatments such as creams or ointments; 12.8% (n = 31) combined treatments. Of the remaining groups, seven (2.9%) received no treatment and two (0.8%) did not specify the route of administration (Table 1).

The majority of these studies 74% (n = 78) were published after the launch of CONSORT in 2001, enrolling 9011 patients (78%); 50% of the studies had been conducted by 2008 and 50% of patients enrolled by 2011 (Table 1 and Figure 2). Studies enrolled on average of 109 patients, ranging from 10 to 444. The average number of patients enrolled per year was 109, with a minimum of 55 in 2000 (excluding 1994, no study published) and a maximum of 160 in 2013 (Figure 3).

Eligibility criteria adopted by the studies

Tables 2 and 3 present all inclusion and exclusion criteria identified by this systematic review classed by trial category, taking into account their date of publication (before or after 2001).

Inclusion criteria

Sex was considered an inclusion criterion in 94.3% (n = 100) of studies enrolling 11 081 patients; 87.7% (n = 93) enrolled participants of both sexes [18–110], seven studies (6.6%) enrolled only men [111–117]; in five studies (4.7%), although sex was not specified in the inclusion criteria, inclusions can be derived from the results [118–122], and one study did not refer to the sex of the participants [123] (Table 2). For pregnancy and lactation, see Exclusion criteria below (Table 3).

Age was an eligibility criterion in 68.9% (n = 73) of the trials. Of these, 32 defined the minimum age for enrolment, which included for 15 studies (20.5%) preschool-aged children (2–5 years old), for seven (9.6%) school-aged children (6–12 years), for six (8.2%) adolescents (13–17 years) and for four (5.4%) adults only (18 years or more). Two studies (2.7%) had only an upper limit which was <18 and ≤60 years. An age range was defined 50.7% (n = 37) of the studies, which was between 2 and 88 years; 5 and 12 years were the most frequent lower limit (7 (9.6%) studies each); 60 years was the most common upper limit (21.9% (n = 16) of studies). Two studies (2.7%) included children without specifying the age range. The proportion of studies enrolling children under 12 years of age increased after the year 2000 (Table 2).

All studies but one [75] (99%, n = 105) required parasitological confirmation of *Leishmania* infection using at least one technique (direct, culture, histopathology, molecular) and 10 (9.5%) included clinical and epidemiological consistency in the diagnosis. Species identification

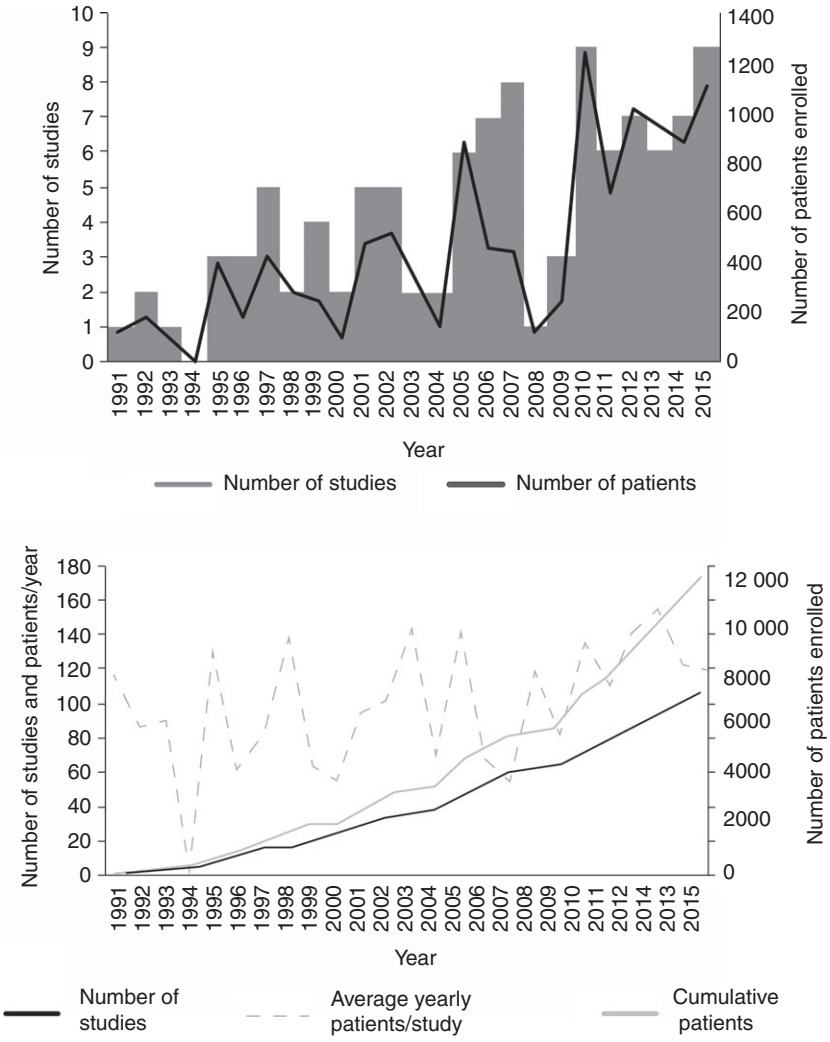

Figure 3 Yearly and cumulative number of studies conducted and patients enrolled during 1991–2015 with average number of patients per year.

was required in 20 studies (19%), but only one did so for all study participants [62] (Table 2). An additional 19 studies (17.9%), while not identifying species, reported the most prevalent species in the study area [22, 25, 34, 48, 50, 51, 58, 72, 78, 81, 84, 85, 101–104, 108, 118, 119] (Table 2).

Duration of the lesion prior to enrolment was specified in 46 studies (43.4%). Of these, 37 (80.4%) published after 2001 limited eligibility to patients whose lesions had appeared between 2 weeks and one year prior to screening, and in 18 (39.1%) studies, this time was 3 months; conversely, three studies (6.5%) required a minimum duration of 1 [52], 3 [89] and 4 [44] months; another two studies (4.3%) required the lesions to have appeared within 2 weeks to 3 months [73] and 1–3 months [59] (Table 2).

Size of the lesion(s) was defined in 28.3% of studies (n = 30) using the mean diameters (n = 23) 76.7% and surface area (n = 7) 23.3%; 53.3% of these (n = 16) accepted lesions 3–5 cm in diameter (Table 2).

Type of lesions was considered in 13.2% (n = 14) of studies; all included ulcerated lesions, but while nine (64.3%) also allowed all other types of lesions, five (35.7%) restricted inclusions to ulcers. Of note, one study limited enrolment to ulcerated lesions for only one of the two topical treatment groups (local application of liquid solution composed of thioxolone and 3 mg benzoxonium chloride + cryotherapy) (Table 2) [93].

Number of lesions was defined in 46.2% (n = 49) of studies, ranging from 1 to 20; 79.6% (n = 39) allowed participants with no more than five lesions, and one

Table 2 Inclusion criteria reported in reviewed studies

		Pre-CONSORT 2001 (28 studies)		Post-CONSORT 2001 (78 studies)	
Criteria (# studies/Total (%))	Categories	Sample size/Total studied 2520 (%)	Reference	Sample size/Total studied 9011 (%)	Reference
Sex (100/106 (94.3))	Both	2300/2510 (91.6)	[18, 19, 22, 23, 26–40, 100, 101, 108–110]	7698/9011 (85.4)	[20, 21, 24, 25, 41–99, 102–107]
	Only men	164/2510 (6.5)	[111, 112]	979/9011 (10.9)	[113–117]
	Inferred from according results	46/2510 (1.8)	[118]	334/9011 (3.7)	[119–122]
Age 73/106 (68.9%)	From preschool-age children (2–5 years)	347/1774 (19.6)	[22, 39]	1919/6112 (31.4)	[20, 21, 41, 49, 58, 60, 63, 77, 82, 84, 89, 90, 93]
	From school-age children (6–12 years)	–	–	539/6112 (8.8)	[56, 59, 65, 78, 79, 85, 119]
	From Adolescents (13–17 years)	33/1774 (1.9)	[19]	616/6112 (10.1)	[57, 61, 71, 95, 102]
	≥18 years	20/1774 (1.1)	[27]	381/6112 (6.2)	[51, 55, 87]
	<18 years	136/1774 (7.7)	[38]	–	–
	≤60 years	137/1774 (7.7)	[32]	–	–
	2–12 years	–	–	116/6112 (1.9)	[81]
	2–60 years	115/1774 (6.5)	[23]	80/6112 (1.3)	[94]
	2–65 years	–	–	90/6112 (1.5)	[66]
	5–50 years	–	–	60/6112 (1)	[75]
	5–60 years	–	–	120/6112 (2)	[44]
	5–65 years	–	–	245/6112 (4)	[52, 74, 98]
	5–75 years	–	–	170/6112 (2.8)	[25, 54]
	6–60 years	182/1774 (10.3)	[31]	165/6112 (2.7)	[88]
	6–65 years	–	–	60/6112 (1)	[91]
	6–75 years	–	–	375/6112 (6.1)	[24]
	7–60 years	127/1774 (7.2)	[101]	225/6112 (3.7)	[69, 80]
	7–70 years	–	–	214/6112 (3.5)	[106, 107]
	8–88 years	63/1774 (3.6)	[36]	–	–
	10–50 years	20/1774 (1.1)	[34]	–	–
	10–60 years	76/1774 (4.3)	[37]	–	–
	12–45 years	44/1774 (2.5)	[28, 123]	–	–
	12–60 years	62/1774 (3.5)	[26]	474/6112 (7.8)	[46, 48, 83, 104]
	14–65 years	–	–	127/6112 (2.1)	[43, 86]
	15–40 years	–	–	36/6112 (0.6)	[67]
	15–50 years	–	–	20/6112 (0.3)	[45]
	18–60 years	242/1774 (13.6)	[33, 112]	80/6112 (1.3)	[103]
	Very young children for whom no local injection was attempted	104/1774 (5.9)	[40]	–	–
	Children	66/1774 (3.7)	[18]	–	–
Diagnosis 105/106 (99.1)	Parasitological	2191/2520 (86.9)	[18, 19, 22, 23, 26–34, 36–38, 40, 100, 108–112]	8432/8951 (94.2)	[20, 21, 24, 25, 41, 42, 44–63, 65–69, 71–74, 76–97, 99, 102, 104–107, 113–120, 122]
	Parasitological + clinical and epidemiological consistency	329/2520 (13.1)	[35, 39, 101, 123]	519/8951 (5.8)	[43, 64, 70, 98, 103, 121]

Table 2 (*Continued*)

Criteria (# studies/Total (%))	Categories	Pre-CONSORT 2001 (28 studies) Sample size/Total studied 2520 (%)	Reference	Post-CONSORT 2001 (78 studies) Sample size/Total studied 9011 (%)	Reference
Species identification 20/106 (18.9)	Species identification	714	[23, 32, 33, 37, 38, 109]	2271	[42, 43, 49, 57, 62, 71, 73, 77, 86, 90, 96, 114–116]
Duration of the lesion prior to enrolment 46/106 (43.4%)	One month and two weeks	–	–	200/3164 (6.2)	[48]
	< 2 months	20/829 (2.4)	[34]	72/3164 (2.3)	[46]
	≤ 2 months	–	–	90/3164 (2.8)	[20, 64]
	< 3 months		–	299/3164 (9.5)	[61, 66, 67, 70, 80, 117]
	≤ 3 months	167/829 (20.1)	[30, 40]	845/3164 (26.7)	[54, 57, 75, 78, 83, 96, 99, 106, 107, 119]
	< 4 months	251/829 (30.3)	[22]	183/3164 (5.8)	[71, 79]
	≤ 4 months	135/829 (16.3)	[23, 27]	288/3164 (9.1)	[21, 41]
	< 6 months	189/829 (22.8)	[26, 101]	339/3164 (10.7)	[58, 72, 76, 94]
	≤ 6 months	67/829 (8.1)	[100]	–	–
	≤ 9 months	–	–	75/3164 (2.4)	[74]
	< 12 months	–	–	60/3164 (1.9)	[88]
	≤ 12 months	–	–	238/3164 (7.5)	[69, 93]
	>One month	–	–	80/3164 (2.5)	[52]
	>3 months	–	–	60/3164 (1.9)	[89]
	> 4 months	–	–	120/3164 (3.8)	[44]
	2 weeks–3 months	–	–	185/3164 (5.8)	[73]
	One month–3 months	–	–	30/3164 (0.9)	[59]
Size lesions 30/106 (28.3)	≤10 cm	–	–	37/2638 (1.4)	[51]
	≤6 cm	–	–	25/2638 (0.9)	[92]
	≤5 cm	191/580 (32.9)	[23, 37]	554/2638 (21)	[46, 63, 83, 89, 104]
	≤4 cm	251/580 (43.3)	[22]	276/2638 (10.5)	[21, 117]
	≤3 cm	–	–	791/2638 (30)	[48, 54, 69, 74, 85, 88]
	≤2 cm	–	–	60/2638 (2.3)	[20]
	≥1 cm –≤5 cm	34/580 (5.9)	[28]	555/2638 (21)	[24, 66, 70]
	≤25 cm^2	–	–	140/2638 (5.3)	[47, 52, 55]
	≤20 cm^2	–	–	45/2638 (1.7)	[113]
	≤10 cm^2	–	–	65/2638 (2.5)	[99]
	≤4 cm^2	104/580 (17.9)	[40]	–	–
	≥1 cm^2 –≤5 cm^2	–	–	90/2638 (3.4)	[25]
Type of lesions 14/106 (13.2)	Only ulcerated	34/357 (9.5)	[28]	345/1422 (24.3)	[25, 44, 66, 113]
	At least one lesion ulcerated	72/357 (20.2)	[111]	275/1422 (19.3)	[70, 73]
	Index lesion ulcerated	–	–	375/1422 (26.4)	[24]
	Ulcerated, nodural and/or papular	251/357 (70.3)	[22]	380/1422 (26.7)	[63, 90, 92]
	Ulcerated lesions in a specific treatment group	–	–	47/1422 (3.3)	[93]
Number of lesions 49/106 (46.2)	One lesion	386/1025 (37.7)	[22, 23, 34]	1256/4786 (26.2)	[20, 21, 49, 82, 85, 119]
	Up to 2 lesions	–	–	523/4786 (10.9)	[51, 63, 69, 74]
	Up to 3 lesions	101/1025 (9.9)	[28, 100]	214/4786 (4.5)	[44, 80, 117]
	Up to 4 lesions	204/1025 (19.9)	[37, 101]	338/4786 (7.1)	[65, 77, 89]
	Up to 5 lesions	158/1025 (15.4)	[26, 35]	1567/4786 (32.7)	

Table 2 (*Continued*)

Criteria (# studies/Total (%))	Categories	Pre-CONSORT 2001 (28 studies) Sample size/Total studied 2520 (%)	Reference	Post-CONSORT 2001 (78 studies) Sample size/Total studied 9011 (%)	Reference
					[24, 25, 46, 48, 54, 66, 70, 75, 78, 83, 88, 92, 93, 104]
	Up to 6 lesions	–	–	473/4786 (9.9)	[52, 73, 86, 96]
	Up to 10 lesions	–	–	359/4786 (7.5)	[71, 84, 102]
	Up to 20 lesions	–	–	56/4786 (1.2)	[62]
	6 or more lesions	104/1025 (10.1)	[40]	–	–
	One or very few lesions	72/1025 (7)	[30]	–	–

required at least 6 [40]. One study restricted inclusion to patients with 'very few' lesions [30] (Table 2).

Exclusion criteria

Anatomical location was restricted in 29 studies (27.4%), 75.8% (n = 22) of which excluded cases with facial lesions (close to or on the nose, eyes, lips and/or ears) (Table 3).

Pregnant and lactating women were excluded in 74 of the 100 studies that enrolled both men and women, of which 30 (40.5%) evaluated systemic therapies, 28 (37.8%) evaluated local therapies, 15 (20.3%) included both routes of administration, and one study did not specify the route of administration; six required contraception for inclusion of women of childbearing age, and of these, four evaluated systemic therapies, one topical and one both routes of administration (Table 3).

Fifteen studies (14.2%) excluded patients with a previous history of CL (Table 3); 72 studies (67.9%) considered eligible patients who had received previous treatment for CL, while 41 (56.9%) excluded them (Table 3).

Altered laboratory values and ECG were exclusion criteria in 54 (50.9%, of which 22 (40.7%) specified haematology, liver and renal functions) and 15 (14.2%) studies, respectively. All studies that included ECG had antimonial treatment in at least one arm (Table 3).

Other exclusion criteria such as mucosal involvement, known hypersensitivity to the drugs used in the study, severe underlying disease and/or different clinical manifestations of CL were applied in 55.7% of the studies.

Treatment outcome assessment

Table 4 presents follow-up times and outcome measures according to the categories reported in the different studies and according to whether they had been conducted before or after the publication of the CONSORT statement.

Follow-up time (reported in 105 studies) ranged from 1 to 24 months, counting from either the beginning or the end of treatment. Overall, 6 months was the most common duration, adopted in 32 studies (30.5%), of which 65.6% from the end of treatment; 50% of the studies conducted after 2001. Only one study did not report duration of follow-up [67] (Table 4a).

In terms of efficacy outcomes, 15 studies (14.2%) specifically defined initial cure, and 96 (90.6%) defined final cure (Table 4b). Although complete re-epithelisation of the ulcer was the definition of 'cure' in 100% and 86.5% of the studies which included initial and definitive cure, respectively, additional criteria were variably present, including absence of active lesion, negative parasitology, 'complete improvement' (lesions flattened, no induration, epidermal creases) and/or reversible hypopigmentation. In 11 studies (11.6%), definitive cure was defined as re-epithelisation >60% [30, 40, 92, 99, 120], >75% [72, 83, 94, 104], >80% [97] or >90% [19] (Table 4c). For all the studies including nodular and papular lesions, cure was defined as resolution and flattening of the lesion.

CONSORT guidelines

Of the 78 studies (73.6%) published after 2001, 62 (80%) appear to follow the CONSORT guidelines on reporting on methods for assigning patients to treatment, explanation of rationale, eligibility criteria, interventions, statistical methods. Though not included in the CONSORT statement, we analysed articles for reporting on ethics and found that 95% of studies did so (Tables 5 and Fig 4).

Table 3 Exclusion criteria reported in reviewed studies

Criteria (# Studies/ Total (%))	Categories[1]	Pre-CONSORT 2001 (28 studies) Sample size/Total studied 2520 (%)	Reference	Post-CONSORT 2001 (78 studies) Sample size/Total studied 9011 (%)	Reference
Anatomical location[2] 29/106 (27.4)	Ears	–	–	–	[71, 80, 88]
	Face	–	[100]	–	[25, 46, 48, 60, 69, 71, 78, 79]
	Near eyes (~2 cm)	–	[31]	–	[49, 54, 75, 80, 82, 90, 99, 114–116, 119, 120]
	Near lips (~2 cm)	–	–	–	[49, 82, 85, 90, 114–116, 119]
	Near nose (~2 cm)	–	–	–	[49, 80, 82, 85, 90, 114–116, 119]
	Near joints	–	–	–	[46, 67, 69, 80, 117]
	Near mucosae	–	[31, 32]	–	[46, 48, 114–116]
	Vital organs	–	–	–	[117]
	Urogenital orifices	–	–	–	[114–116]
	Lesions in 2 or more anatomical locations	–	–	–	[66]
Pregnant and/or lactating women 74/100 (74)	Excluded	1403	[19, 22, 23, 28, 29, 31, 32, 34–36, 38, 39, 101, 108, 109]	5482	[21, 24, 25, 41, 43–49, 51–60, 62–64, 66, 67, 69–72, 74–76, 79, 80, 83, 84, 86–99, 102–107, 120, 121]
Women of childbearing age 9/100 (9)	Yes	20	[27]	239/800 (29.9)	[59, 102]
	Yes, but with contraception	–	–	561/800 (70.1)	[46, 48, 52, 62, 70, 105]
Previous history of CL 15/106 (14.2)	Yes	622	[22, 30, 40, 100, 101]	1353	[49, 51, 66, 67, 80, 82, 90, 99, 103, 105]
Previous treatment 72/106 (67.9)	Yes[3]	–	–	40/7033 (0.6)	[47]
	No	370/1110 (33.3)	[27, 28, 37, 38, 40]	4566/7033 (64.9)	[20, 21, 27, 41–43, 48, 49, 51–53, 55, 60, 63, 66, 67, 69, 70, 75, 79, 80, 82, 83, 90, 93, 96, 99, 103–107, 114–117, 119]
	No, last month	72/1110 (6.5)	[111]	634/7033 (7.5)	[46, 74, 76, 81, 89, 91, 92, 98, 120]
	No, last 2 months	–	–	489/7033 (6.4)	[77, 84, 102, 121]
	No, last 3 months	–	–	956/7033 (11.7)	[25, 57, 58, 65, 72, 85, 87, 94]
	No, last 6 months	668/110 (60.2)	[31, 32, 36, 100, 101, 112]	348/7033 (4.3)	[73, 95]
Altered laboratory values 54/106 (50.9)	Haematologic + renal + liver + pancreatic function	–	–	704/3980 (17.7)	[57, 62, 81, 87, 95]
	Haematologic + renal+ liver function	904/1559 (58)	[22, 23, 31, 35, 39, 111, 112]	1581/3980 (39.7)	[56, 59, 64, 66, 67, 78, 84, 94, 103, 105, 114–116, 121, 122]
	Haematologic + renal function	–	–	63/3980 (1.6)	[53]
	Haematologic + liver function	186/1559 (11.9)	[27, 110, 118]	122/3980 (3.1)	[41, 50]
	Renal + liver function	163/1559 (10.5)	[26, 28, 100]	750/3980 (18.8)	[21, 55, 71, 73, 102]
	Renal, liver and pancreatic function	63/1559 (4)	[36]	230/3980 (5.8)	[52, 91, 98]
	Renal function	–	–	45/3980 (1.1)	[113]

Table 3 (*Continued*)

Criteria (# Studies/ Total (%))	Categories[1]	Pre-CONSORT 2001 (28 studies)		Post-CONSORT 2001 (78 studies)	
		Sample size/Total studied 2520 (%)	Reference	Sample size/Total studied 9011 (%)	Reference
	Laboratory test (haematologic and/or blood chemistry)	243/1559 (15.6)	[19, 108, 109]	485/3980 (12.2)	[42–44, 48, 86]
Altered electrocardiogram 15/106 (14.2)	Yes	235	[26, 36, 108]	1075	[43, 44, 52, 53, 57, 62, 64, 86, 87, 91, 98, 103]

[1]An affirmative answer in any of the categories, was considered compliance with the criteria exclusion.
[2]Due to that in many of the studies were considered more of one anatomical location, for this exclusion criteria, sample size/total studied (%) was not calculated.
[3]A negative answer in this specific item was considered as compliance with the exclusion criterion.

Discussion

This systematic review provides an overview of how participants were selected and treatment effects were assessed in therapeutic trials of OWCL and NWCL published between 1991 and 2015. Overall, we found 106 trials, which enrolled 11 531 participants in 243 treatment groups. These studies were conducted in 24 countries, which correspond to approximately one-fourth of the countries endemic for CL worldwide [1, 3], being collectively responsible for one-third of the global estimated current burden of CL [124].

This landscape analysis scrutinises the range of criteria used by investigators to select participants and to assess how treatment works in order to account more accurately for the main sources of the heterogeneity in trial outcomes reported by previous systematic reviews [12]. Inconsistent methodologies have been identified as the reason why CL treatment guidelines are based on weak evidence. The present review includes 61% [12], 47% [8] and 80% [11] of papers included in previous reviews, and 53 more.

Drawing generalisable conclusions and making treatment recommendations is no easy task, as CL is not just one disease. The paucity and fragmentation of information make this task all the more difficult. Not counting 38 articles that could not be recovered, just over 100 trials and 11 000 patients studied in almost a quarter of a century is not much for a disease that would have affected some 25 million people during the that period. To this must be added the complexity of this disease in terms of the causative *Leishmania* species and the resulting differences in the natural history and evolution of disease, as well as response to treatment. Here, 68 and 38 were on OWCL and NWCL, respectively, and the causative species was identified in less than one-fifth of the studies (12 NWCL and eight OWCL). Also, 30 treatments were tested in 243 treatment groups (115 systemic, 88 topical and 31 combined; unknown or untreated for the remaining 9). Together, these elements explain the fragmentation of the evidence produced by these studies and the resulting paucity of effective treatments that can be recommended for use with enough confidence that they will work.

The CONSORT statement introduced a set of criteria aimed at improving the quality of clinical research reports [15–17]. As approximately two-thirds of both studies and participants were from articles published after 2001, one would expect quality to have improved since. Of note, half of the studies were conducted by 2006 and half of the participants recruited by 2010, meaning that they tend to concentrate in more recent years. The

Table 4 Follow-up time and outcome measure

(a) Duration of follow-up

	Count from treatment				
Time	Start	End	NR	From cure	Total
4 weeks	2	6	–	–	8
5 weeks	–	1	–	–	1
6 weeks	2	3	1	–	6
8 weeks	1	3	3	–	7
9 weeks	–	1	–	–	1
10 weeks	1	–	–	–	1
3 months	4	10	1	–	15
100 days	–	1	–	–	1
105 days	2	1	–	–	3
110 days	2	–	–	–	2
4 months	2	1	2	–	5
5 months	–	1	–	–	1
6 months	6	23	–	3	32
168 days	1	1	–	–	2
12 months	4	12	1	–	17
18 months	–	1	–	1	2
24 months	–	1	–	–	1
Total	27	66	8	4	105

(b) Outcome definitions

Outcome	Initial cure	Final cure
Complete re-epithelisation	4	15
Complete re-epithelisation **WITHOUT** any activity signs	10	26
Complete re-epithelisation **WITHOUT** relapse	–	9
Complete re-epithelisation **WITHOUT** any activity signs + negative parasitology test	–	6
Complete re-epithelisation **AND** negative parasitology test	–	7
Complete re-epithelisation **OR** clinical improvement	1	3
Complete re-epithelisation **OR** clinical improvement + negative parasitology test	–	2
Complete re-epithelisation **WITH** reversible hypopigmentation	–	3
Initial cure **WITHOUT** relapse	NA	11
Initial cure **WITHOUT** appearance of new lesions	NA	1
Clinical improvement	–	7
Clinical improvement **AND** negative parasitology test	–	6
Total	15	96

Table 4 (*Continued*)

(c) Outcome measure reported in reviewed studies

Criteria (# studies/ Total (%))	Categories		Before CONSORT statement (28 studies)		After CONSORT statement (78 studies)	
			Sample Size/Total studied 2520 (%)	Reference	Sample Size/Total studied 9011 (%)	Reference
Follow-up time 105/106 (99.1)	4 weeks	From beginning of treatment	67/2520 (2.7)	[100]	37/8975 (0.4)	[51]
		From end of treatment	304/2520 (12.1)	[18, 29, 110, 118]	222/8975 (2.5)	[41, 121]
	5 weeks	From end of treatment	–	–	72/8975 (0.8)	[46]
	6 weeks	From beginning of treatment	–	–	170/89751.9)	[50, 71]
		From end of treatment	63/2520 (2.5)	[30]	125/89751.4)	[76, 92]
		Not specified	104/2520 (4.3)	[40]	–	–
	8 weeks	From beginning of treatment	–	–	160/8975 (1.8)	[96]
		From end of treatment	96/2520 (3.8)	[35]	131/8975 (1.5)	[20, 78]
		Not specified	–	–	161/8975 (1.8)	[80, 99, 122]
	9 weeks	From end of treatment	10/2520 (0.4)	[123]	–	–
	10 weeks	From beginning of treatment	137/2520 (5.4)	[32]	–	–
	3 months	From beginning of treatment	–	–	425/8975 (4.7)	[65, 79, 89, 107]
		From end of treatment	20/2520 (0.8)	[27]	831/8975 (9.3)	[48, 53–55, 74, 91, 94, 95, 98]
		Not specified	–	–	30/89757 (0.3)	[56]
	4 months	From beginning of treatment	–	–	356/89757 (4)	[69, 88]
		From end of treatment	–	–	119/8975 (1.3)	[104]
		Not specified	–	–	139/8975 (1.5)	[58, 106]
	5 months	From end of treatment	–	–	83/8975 (0.9)	[83]
	6 months	From beginning of treatment	92/2520 (3.7)	[34, 111]	338/8975 (3.8)	[25, 81, 113, 119]
		From beginning of treatment	129/2520 (5.1)	[19, 39]	2969/8975 (33.1)	[59–61, 63, 64, 66, 70, 72, 73, 75, 82, 85–87, 93, 103, 105, 114–117]
		After cure	–	–	614/8975 (6.8)	[90, 97, 120]
	12 months	From beginning of treatment	170/2520 (6.7)	[28, 38]	140/8975 (1.6)	[44, 45]
		From end of treatment	710/2520 (28.2)	[31, 33, 37, 108, 109, 112]	491/8975 (5.5)	[42, 43, 47, 52, 57, 102]
		No specified	62/2520 (2.5)	[26]	–	–
	18 months	From end of treatment	–	–	100/8975 (1.1)	[77]
		After cure	–	–	154/8975 (1.7)	[68]
	24 months	From end of treatment	–	–	56/8975 (0.6)	[62]
	100 days	From beginning of treatment	–	–	431/8975 (4.8)	[49]
	105 days	From beginning of treatment	366/2520 (14.5)	[22, 23]	2168975 (2.4)	[21]
	110 days	From beginning of treatment	190/2520 (7.5)	[36, 101]	–	–

Table 4 (*Continued*)

(c) Outcome measure reported in reviewed studies

Criteria (# studies/ Total (%))	Categories		Before CONSORT statement (28 studies)		After CONSORT statement (78 studies)	
			Sample Size/Total studied 2520 (%)	Reference	Sample Size/Total studied 9011 (%)	Reference
	168 days	From beginning of treatment	–	–	375/8975 (4.2)	[24]
		From end of treatment	–	–	30/8975 (0.3)	[84]
Initial cure (15/106 (14.2))	Complete re-epithelisation	At end of treatment	178/650 (27.4)	[23, 36]	–	–
		1.5 months after treatment	150/650 (23.1)	[33]	–	
		2 months after treatment, without activity signs	–	–	305/1718 (17.8)	[66, 73, 84]
		3 months after treatment	110/650 (16.9)	[108]	–	–
		3 months after treatment without signs	–	–	922/1718 (53.7)	[86, 114–116]
		1 month after treatment or clinical improvement with scar 10 weeks after end of treatment	–	–	375/1718 (21.8)	[24]
		13 weeks from treatment start without activity signs	212/650 (32.6)	[37, 38]	116/1718 (6.8)	[81]
Final cure (96/106 (90.6))	Complete re-epithelisation		20/2217 (0.9)	[34]	2479/9791 (25.3)	[41, 42, 45, 48, 54, 62, 63, 68, 71, 77, 85, 90, 103]
	Complete re-epithelisation	Without relapse at end of follow-up	778/2217 (35.1)	[18, 22, 23, 31, 111, 112]	165/9791 (1.7)	[44, 113]
		Without activity signs at end of follow-up	159/2217 (7.2)	[36, 39]	1093/9791 (11.2)	[25, 43, 49, 52, 66, 70, 73, 86]
		Without activity signs	274/2217 (12.4)	[32, 101, 123]	1593/9791 (16.3)	[47, 49, 55, 56, 67, 78, 79, 82, 93, 95, 96, 121]
		With reversible hypopigmentation	118/2217 (5.3)	[29, 118]	50/9791 (0.5)	[50]
		With negative parasitology test	87/2217 (3.9)	[27, 100]	469/9791 (4.8)	[59, 88, 91, 98, 107]
		Without activity signs and negative parasitology test	100/2217 (4.5)	[109]	360/9791 (3.8)	[20, 61, 64, 69, 74]
		1 week after end of treatment	–	–	60/9791 (0.6)	[117]
		Or >50% re-epithelisation + negative parasitology test	–	–	216/9791 (2.2)	[21]
		Or clinical improvement >75%	–	–	100/9791 (1.0)	[76]
		Or clinical improvement >75% + negative parasitology test	–	–	49/9791 (0.5)	[58]
		Without activity signs at three moths post treatment	–	–	63/9791 (0.6)	[105]

Table 4 (*Continued*)

(c) Outcome measure reported in reviewed studies

Criteria (# studies/ Total (%))	Categories	Before CONSORT statement (28 studies)		After CONSORT statement (78 studies)	
		Sample Size/Total studied 2520 (%)	Reference	Sample Size/Total studied 9011 (%)	Reference
	Or >50% reduction of induration and ulceration vs. previous visit	–	–	324/9791 (3.3)	[87]
	Marked reduction of induration with or without scar	–	–	72/9791 (0.7)	[46]
	Before day 75 after treatment start	–	–	87/9791 (0.9)	[119]
Initial cure	Without relapse	472/2217 (21.3)	[33, 37, 38, 108]	1417/9704 (14.6)	[24, 66, 84, 86, 114–116]
	Without appearance of new lesions	–	–	116/9704 (1.2)	[81]
Decrease in induration size >75%		–	–	190/9704 (2)	[72, 94]
	No activity signs and epidermal creases appeared	–	–	180/9704 (1.9)	[53, 60]
	>75% reduction at 8 week compared with baseline	–	–	202/9704 (2.1)	[83, 104]
	>90% improvement and negative parasitology test	33/2217 (1.5)	[19]	–	–
	>80% improvement and negative parasitology test	–	–	444/9704 (4.6)	[97]
	>60% improvement and negative parasitology test	176/2217 (7.9)	[30, 40]	100/9704 (1.0)	[99, 120]
	>60% improvement	–	–	25/9704 (0.3)	[92]

Table 5 Compliance to CONSORT statement

CONSORT period	Overall 2002–2015	Period 1 2002–2010	Period 2 2011–2015	Difference
Number of studies published in the period	78	43	35	–
Criteria	%(# studies)	%(# studies)	%(# studies)	% period 2–% Period 1
Patient allocation (title)	41 (32)	39.5 (17)	42.9 (15)	3.3
Patient allocation (abstract)	85.9 (67)	81.4 (35)	91.4 (32)	10
Abstract structured	NA	NA	71.4 (25)	NA
Scientific background	100 (78)	100 (43)	100 (35)	0
Explanation of rationale	93.6 (73)	90.7 (39)	97.1 (34)	6.4
Trial design	NA	NA	68.6 (24)	NA
Participants (eligibility criteria, setting and location)	96.2 (75)	95.3 (41)	97.1 (34)	1.8
Interventions	100 (78)	100 (43)	100 (35)	–
Objectives/hypotheses	NA	4.7 (2)	NA	NA
Outcome	97.4 (76)	97.7 (42)	97.1 (34)	−0.5
Sample size	46.2 (36)	39.5 (17)	54.3 (19)	14.8
Randomisation sequence generation	37.2 (29)	32.6 (14)	42.9 (15)	10.3
Randomisation sequence allocation/concealment	23.1 (18)	20.9 (9)	25.7 (9)	4.8
Randomisation implementation	25.6 (20)	16.3 (7)	37.1 (13)	20.9
Blinding	73.1 (57)	74.4 (32)	71.4 (25)	−3.0
Statistical methods	88.5 (69)	88.4 (38)	88.6 (31)	0.2
Flow diagram	35.9 (28)	32.6 (14)	40 (14)	7.4
Recruitment	75.6 (59)	62.8 (27)	91.4 (32)	28.6
Baseline data	94.9 (74)	97.7 (42)	91.4 (32)	−6.3
# patients analysed	56.4 (44)	51.2 (22)	62.9 (22)	11.7
Outcomes and estimation	97.4 (76)	97.7 (42)	97.1 (34)	−0.5
Ancillary analyses	33.3 (26)	14 (6)	57.1 (20)	43.2
Safety	75.6 (59)	74.4 (32)	77.1 (27)	2.7
Additional analysis				
Number of studies published in the period	78	43	35	–
Criteria	%(# studies)	%(# studies)	%(# studies)	% period 1–% Period 2
Methods section structured	65.4 (51)	65.1 (28)	65.7 (23)	0.6
Results section structured	29.5 (23)	25.6 (11)	34.3 (12)	8.7
Ethics aspects	94.9 (74)	90.7 (39)	100 (35)	9.3

quality in reporting clinical trials has increased over time; the temporal analysis of adherence to the CONSORT statement, regarding its first (2001) [15–17] and second (2010) [125] version, shows an increase in the reporting on most criteria such as patient allocation, sample size calculation, treatment allocation and ancillary analysis. In addition, approximately two-thirds and one-third of the papers, respectively, were structured with clear sections and subsections for materials and methods (ethical statement, design, participants, treatments, etc.) and results (baseline data, efficacy, safety outcomes, etc.).

Despite this positive trend, overall we found that studies adopted a range of eligibility criteria and outcome measures and that basic requirements in the definitions were not always present or varied across the studies.

As for demographics, the admissible age was specified in just over two-thirds of the studies, in which varying age ranges were defined; the proportion of children enrolled increased after 2001; 94% of studies specified the sex of participants. Equal opportunities were offered to both genders in 95% of cases, limited to non-pregnant, non-lactating women in 74% of these.

Reassuringly, parasitological confirmation was required in all studies but one. However, there were inconsistencies as to elements related to the natural history of disease which would affect response to treatment [4]. Species identification was required in only 19% of studies (11.1% and 32.5% of those on OWCL and NWCL, respectively), but was not conducted on all patients enrolled. Previous duration of illness was defined in just

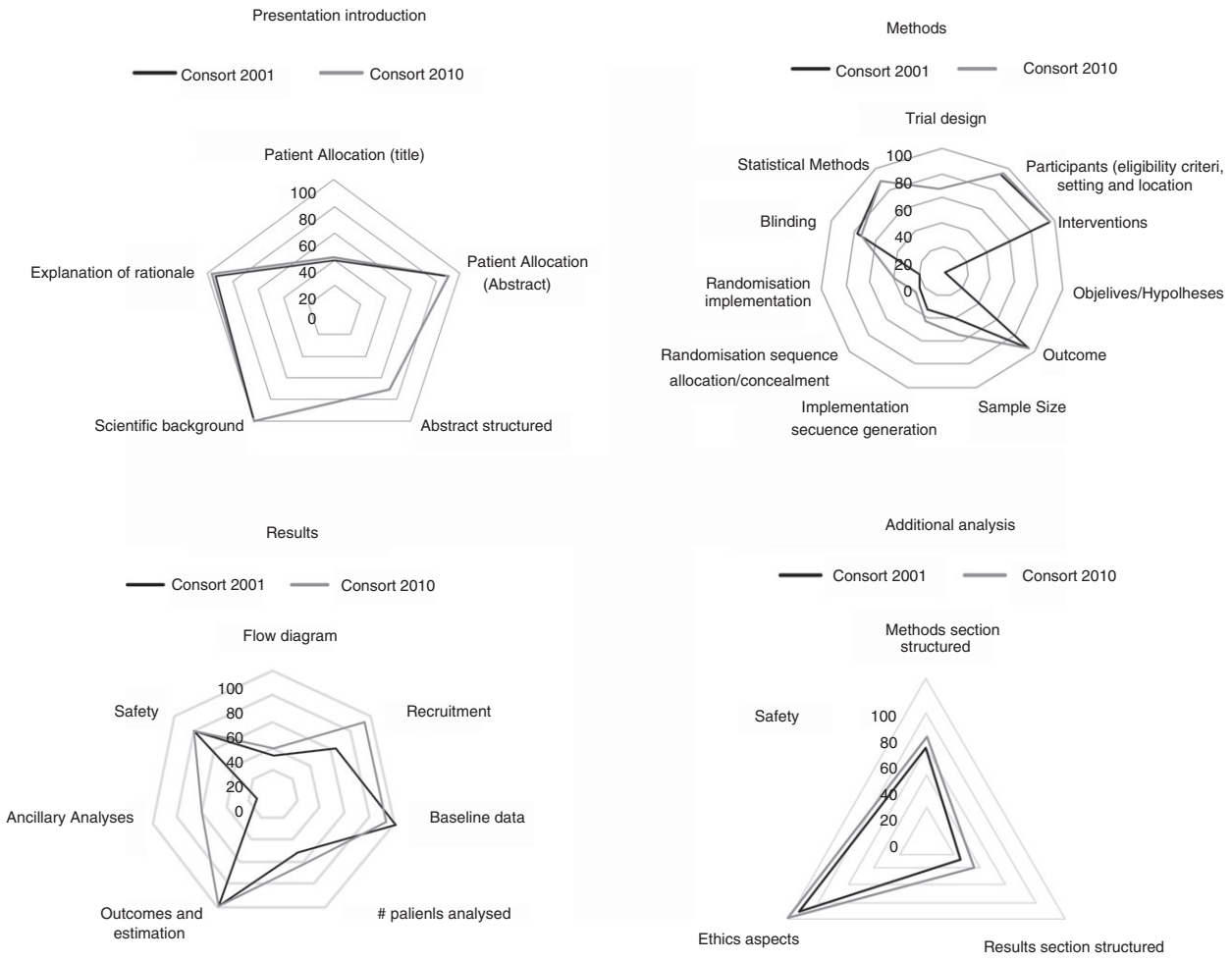

Figure 4 Compliance with CONSORT statement.

under half of studies, mostly published after 2001. This parameter is important with respect, on the one hand, to the tendency of forms like those caused by *L. major* and *L. mexicana* to self-heal over a certain period of time [126, 127], and on the other hand, to the severity, size and number of lesions, which could increase with time in non-self-healing species.

It is also very difficult to compare studies in terms of lesion characterisation, as only 13% defined the type of lesion, 28% their size and 46% their number – the latter would be expected to determine also the choice of the route of administration (systemic or topical). It is estimated that in general, 90% of cases present with fewer than five lesions [128].

When comparing the eligibility and outcome criteria found in this review with those proposed by Olliaro *et al.* 2013 [14], we found only partial consistency. Entry criteria taken into account in most of the trials were as follows: demographic characteristics (age and sex), parasitological confirmation, and exclusion of pregnant and lactating women as well as patients who had already been treated for the ongoing episode of CL, those with lesions close to mucous membranes and/or on the face, those with hypersensitivity to study drug and those with different clinical manifestations to CL. Other, yet important, criteria that were considered only in a minority of studies were as follows: parasite species identification, previous duration, type, number, location and size of lesions, which were present only in 19%, 43%, 13%, 46%, 27% and 28% of the studies, respectively. Concerning outcome measures, the definition of the primary outcome was described in 90% of studies; for

approximately three-quarters of these, the assessment of cure was based on clinical evaluation (complete re-epithelialisation) as in the guidance document [14]. However, it is difficult to provide a more accurate comparison also because the phase of clinical experimentation (whether pre-registration phases 2 and 3, or post-registration phase 4) was rarely reported in the published papers.

In summary, this study provides further evidence of the variable quality of treatment trials in CL; it explores the granularity of the methods and results sections of papers over a 15-year period, and assesses the adequacy of reporting before and after the publication of the CONSORT statement and its subsequent update. Lack of standardisation, compounded with the small number of trials relative to the magnitude of the disease in its multiple forms, and with the range of treatments tested explains why evidence to inform treatment guidelines is generally weak for CL. While improvements have occurred in the quality of reporting, much remains to be done in adhering to standardised methodologies.

Solving the problem of cutaneous leishmaniasis treatment requires both development of therapeutic alternatives and improvements in the quality of evidence. Standardisation of clinical trial methods for the evaluation of CL is necessary to determine effectivity and safety, to compare studies and strength of the evidence, and ultimately lead to better treatment outcomes.

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