Treatment of New World cutaneous leishmaniasis: a systematic review with a meta-analysis

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CRD summary
The authors concluded that although pentavalent antimonial drugs were still effective for patients in Latin America with cutaneous leishmaniasis, cure rates were similar for pentamidine. Evidence appeared to support the authors’ conclusions, but differences between studies and the small number of studies that directly compared treatments may limit the strength of the evidence.

Authors' objectives
To determine the optimal drug treatment for patients in Latin America with cutaneous leishmaniasis.

Searching
MEDLINE, LILACS, EMBASE, Web of Science (all from 1966 to August 2006) and The Cochrane Library (to August 2006) were searched using reported terms. No language restrictions were applied. In addition, reference lists in primary studies and reviews were screened.

Study selection
Studies that evaluated drug treatment of patients with cutaneous leishmaniasis in Latin America were eligible for inclusion. Patients with other forms of leishmaniasis, post-kala-azar cutaneous leishmaniasis, mucosal lesions or more than four cutaneous lesions were excluded. Studies had to present: sufficient information to permit calculation of cure rate (complete lesion cicatrisation persisting for more than three or 12 months after treatment start); treatment failure rate; an assessment of internal and external validity; and report the region and most prevalent species of Leishmania.

The included studies evaluated pentavalent antimonials, pentamidine, paromomycin (including topical and intravenous formulations) and other drugs including allopurinol and imidazole drugs. Most studies were of patients receiving primary treatment. Other studies were in patients with a failed response to primary treatment. Studies established a diagnosis of cutaneous leishmaniasis by analysis of lesion scrapings, aspiration samples or biopsy specimens. Most studies were conducted in Brazil or Columbia.

Two reviewers independently selected studies. Disagreements were resolved by a third reviewer.

Assessment of study quality
Two reviewers independently extracted the following eight internal and external validity-related characteristics: randomisation; blinding; inclusion and exclusion criteria; extent of follow-up; disease presentation; diagnosis method; Leishmania species; and method used for identification. Studies meeting at least six of the eight criteria were classified as high-quality, those meeting at least three were classified as moderate quality and studies scoring less than three were classified as low quality. Disagreements were resolved by consensus.

Data extraction
Efficacy data were extracted from each study. Confidence intervals (CI) were recalculated for each study. Studies were classified as comparative, dose-finding and noncomparative. For comparative studies, odds ratios (OR) with 95% CIs were calculated.

The authors did not state how data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The studies were grouped by drug class. Where possible within each drug class, the treatment effect was reported with respect to country, species, drug, therapeutic duration and use as treatment/re-treatment. Pooled ORs with 95% CIs were calculated for randomised controlled trials (RCTs) that directly compared drugs of interest. Methods used to pool data were not reported.

Results of the review
The authors stated that 54 studies were included in the review (2,969 patients). Twelve RCTs that compared different drugs were included in meta-analysis.

The authors stated that more than 80 per cent of studies had moderate to high quality.

Unless specifically stated otherwise, response rates reported below were from uncontrolled studies.

**Pentavalent antimonials:** The overall cure rate for patients with primary cutaneous leishmaniasis was 76.5 per cent (23 studies, 1,133 patients). For patients receiving 20 doses of 20mg/kg/day of meglumine there were no differences in response between different *Leishmania* species (*L. braziliensis*, *L. amazonensis* and *L. guyanensis*). Results differed across different regions (71.3% in Brazil and 91.4% in Columbia). Meglumine and stibogluconate showed similar response rates (both 76.5%).

**Paromomycin:** For patients infected with any *Leishmania* species pentavalent antimonials (20mg/kg/20 days) had lower response rates than pentamidine (4mg/kg/7 days) with 77 per cent versus 87 per cent, p<0.05. However, meta-analysis of four studies that directly compared the two drugs showed no significant difference. For patients who failed to respond to initial treatment with pentavalent antimonials, pentamidine was associated with a higher response rate than re-treatment with pentavalent antimonials (87.2% versus 63.6%, p<0.05).

**Other drugs:** Cure rates were reported as 38 per cent for intravenous paromomycin (106 patient) and 78 per cent for topical paromomycin. Meta-analysis of controlled studies showed significantly higher response rates for antimonials compared to allopurinol (OR 0.31, 95% CI 0.18 to 0.55; three studies), topical aminoglycosides (paromomycin, OR 0.25, 95% CI 0.12 to 0.49), intravenous paromomycin (OR 0.55, 95% CI 0.31 to 0.99) and imidazole agents (OR 0.02, 95% CI 0.01 to 0.09; two studies). The number of studies of each form of paromomycin was not clear.

**Authors’ conclusions**

Although pentavalent antimonials were still effective for patients in Latin America with cutaneous leishmaniasis, cure rates were similar for pentamidine. Local circumstances needed to be taken into account when selecting the most appropriate drug treatment.

**CRD commentary**

The review question was clearly stated and inclusion criteria defined for intervention, participants and outcome. Several relevant sources were searched. No language restrictions were applied. No specific attempts to minimise publication bias were reported. Appropriate methods were used to minimise reviewer error and bias during study selection and validity assessment, but methods used to extract data were not described, so it was not known whether efforts were made to reduce reviewer error and bias.

The quality of studies was assessed using specified criteria, but quality was not taken into account when reporting findings. There appeared to be some discrepancies between the number of studies reported in the text and the first table. Response rates varied among studies and some attempts were made to examine potential sources of heterogeneity. However, data from controlled studies were combined without any formal assessment of statistical heterogeneity, so it was not clear if pooling data was appropriate.

Evidence appeared to support the authors’ conclusions, but differences between studies and the small number of studies that directly compared treatments may limit the strength of the evidence.

**Implications of the review for practice and research**

**Practice:** The authors stated that cost, adverse effects, local experience and drug availability must be taken into account when selecting drugs to treat cutaneous leishmaniasis especially when resources are scarce.

**Research:** The authors stated that there was a need for further studies to evaluate the sole use of itraconazole for the treatment of leishmaniasis.

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