# Cutaneous leishmaniasis

The Review by Richard Reithinger and colleagues[1] on cutaneous leishmaniasis was a useful update on a neglected but important disease.[2] We would like to make a few comments regarding the treatment section of that article.

Table 2 of the Review[1] provides a summary of the recommended and alternative treatment regimens for cutaneous leishmaniasis. The authors mention that with the exception of studies assessing treatment options for mucosal leishmaniasis, they only included studies in which monotherapies were assessed.[1] There are, however, trials in which outcomes of monotherapy were assessed that are not included in the table.[3–7] In these trials, photodynamic therapy, carbon dioxide laser, rifampicin, and topical ethanolic lipid amphotericin B were reported to be effective in the treatment of cutaneous leishmaniasis, whereas oral allopurinol was not effective.[3–7] Additionally, there are several trials that have assessed the efficacy of combination therapies in the treatment of cutaneous leishmaniasis.[8–10] The rationale behind Reithinger and colleagues' decision is required to explain the potential selection bias in their Review.

In the fourth column of table 2,[1] clinical efficacy against *Leishmania* spp has not been presented in a manner that can be clearly understood. We believe that more detailed description of the included studies and provision of 95% CIs might be a better option. Example of such presentation is available elsewhere.[11] The provided range for some interventions is too wide to be clinically meaningful without further explanation.

Finally, we noticed that despite the efforts of the authors to pay particular attention to articles published in non-English literature, several studies that where done in Iran might have been overlooked.[12,13] The results of these studies are published in Persian, their English abstracts are available in the Cochrane Library, and according to the authors' selection criteria, they appear to be eligible for inclusion.

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We declare that we have no conflicts of interest.

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# Authors' reply

We thank Alireza Khatami and colleagues for pointing out that we inadvertently missed some studies investigating various treatment approaches of cutaneous leishmaniasis in our recent Review of the disease.[1] Indeed, the studies referred to by Khatami and colleagues demonstrate the wealth of clinical trials that have been done in Iran, many of which may not be familiar to researchers and practitioners working on cutaneous leishmaniasis. Thus, according to the criteria set out in our Review,[1] we should have included a study from Iran that presents efficacy data on photodynamic therapy and topical paromomycin

for the treatment of cutaneous leishmaniasis caused by *Leishmania major*.[2]

Khatami and colleagues' critique also shows that—as highlighted in our Review and in a consultative meeting on cutaneous leishmaniasis[1,3]—standard criteria for leishmaniasis clinical trials are urgently needed. Six of the seven studies[4–9] that the authors state should have been included have methodological limitations. First, one study had a smaller sample size than the amount stated as sufficient for inclusion in our Review—ie, ten patients per treatment cohort.[6] Second, studies were non-randomised or did not have inclusion/exclusion criteria.[5,6,8] Third, although these studies included a placebo or pentavalent antimony control arm, those that used a pentavalent antimony control arm used non-standard doses or regimens (eg, 50 mg/kg per day meglumine antimonate for 15 days, repeated after a 15-day window where no treatment was given).[4] Fourth, the parasite species causing disease in individuals enrolled in the trials were not identified.[4,5] Fifth, follow-up was less than 2 months post treatment, making it difficult for comprehensive comparison between the treatment arms,[5,7,9] or follow-up was not specified.[6] Finally, criteria of cure differed between studies, with cure being defined as either "complete re-epithelialisation and parasitological cure", "complete cure", or lesion improvement with "reduction of lesion size by at least 80%".[4–9]

We agree with Khatami and colleagues that research on combination therapies for cutaneous leishmaniasis should be expanded to improve efficacy and patient compliance, decrease treatment cost, and delay the potential development of drug resistance. We decided to exclude combination therapies from our Review largely because the methodological protocols of studies assessing combination therapies are even less standardised than protocols for monotherapy trials, making study comparison virtually impossible.

The studies included in our Review provide a wide range of cure rates for different treatment approaches. However, this shows that, besides a few (recommended) approaches, "one size does not fit all" for cutaneous leishmaniasis treatment. Efficacy of treatment is dependent on several factors—eg, lesion location, size, number, and duration—again, highlighting the need for standardised study protocols to exclude as far as possible such confounding factors from data analysis. Inclusion of 95% CIs would not have changed our recommendations of first-line and alternative treatment approaches for cutaneous leishmaniasis.[1]

A meta-analysis on cutaneous leishmaniasis treatment interventions could—depending on the analyses done—make the best use of existing clinical trial data and yield evidence-based treatment recommendations. However, even meta-analyses can only address some of the above-mentioned methodological deficiencies to compare data on various approaches for cutaneous leishmaniasis treatment. Without developing standardised cutaneous leishmaniasis clinical trial criteria in the near future, comparisons between clinical studies will be of little value and no real measurable progress in treatment will be made.

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