The cure rate after placebo or no therapy in American cutaneous leishmaniasis: a systematic review and meta-analysis

Gláucia F Cota[1]; Marcos R de Sousa[2]; Tatiani O Fereguetti[3]; Priscila S Saleme[3]; Thais K Alvarisa[3]; Ana Rabello[1]

[1]Clinical Research and Public Policy in Infectious and Parasitic Diseases– Centro de Pesquisas René Rachou - Fundação Oswaldo Cruz, Fiocruz, Belo Horizonte, 30.190-002 Minas Gerais, Brazil. E-mail: cota@cpqrr.fiocruz.br. [2]Post-Graduate Program in Adult Health Sciences – Universidade Federal de Minas Gerais, Belo Horizonte, 30130-100 Minas Gerais, Brazil. [3]Hospital Eduardo de Menezes – Fundação Hospitalar do Estado de Minas Gerais-FHEMIG, Belo Horizonte, 30.622-020 Minas Gerais, Brazil

There are few drugs with proven efficacy in cutaneous leishmaniasis (CL), and pentavalent antimonial derivatives are still the main first-line therapeutic agents worldwide, despite their recognized high toxicities. Randomized controlled clinical trials assessing the efficacy and safety of new therapeutic modalities are of high priority, and the definition of the design of such trials raises debate about the use of placebo as a comparator. To support the use of placebo as a comparator, two main points need to be addressed: 1- the cure rate without any therapeutic intervention and 2- the damage caused by CL and its impact on patients. The aim of this study was to systematically assess the spontaneous cure rate for American CL and to broaden the discussion about placebo use in CL trials. The PRISMA guidelines for systematic reviews and the Cochrane manual were followed. The sources used were the PubMed and LILACS databases. Studies were included if they reported cure rates using placebo or no treatment in American CL. Thirteen studies of a total of 352 patients were ultimately included in this review. The summarized global cure rates for all *Leishmania* species according to the intention-to-treat analyses performed at approximately three ("initial cure") and nine ("definitive cure") months after "no treatment" or placebo use were 26% (CI95%: 16 to 40%) and 24% (CI95%: 15 to 37%), respectively. Notably, a significantly lower cure rate was observed for *L. braziliensis* infection (6.4%, CI95%: 0.2 to 20%) than for *L. mexicana* infection (44%, CI95%: 19 to 72%), p = 0.002. Of note, relapse occurred in 18% of patients with initial healing (CI95%: 8.6 to 35.1%). These results clearly demonstrate an irrefutable difference between outcomes following treatment and no-treatment or placebo use, confirming that placebo use and no therapy as strategies for the control group in CL studies expose patients to greater morbidity, especially for CL caused by *L. braziliensis*. Therefore, now, the crucial point to consider regarding placebo use is the seriousness of the suffering caused by this disease.

Keywords: Leishmaniasis, cutaneous; treatment outcome; placebo

Support: CNPq (Grant 311641/2009-1)