TREATMENT FAILURE AND DRUG RESISTANCE IN VISCERAL AND TEGUMENTARY LEISHMANIASES: HOW MANY ROADS MUST A PARASITE WALK DOWN?

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Treatment is a major pillar of leishmaniasis control programs, but the arsenal of available drugs is limited and their use is jeopardized by the emergence of drug resistance. Combination regimens are under clinical development, but it will take several more years to change the drug policy. Meanwhile, the effectiveness of current drugs needs to be safeguarded to ensure unremitting sustainment of leishmaniasis control. Therefore, factors underlying treatment failure need to be better understood. These may be related to (i) the parasite (intrinsic insensitivity -i.e. species- or drug resistance), (ii) the treatment (drug quality, compliance, dosage), and (iii) the host (clinical presentation, immunological response, host genetics). We present here a review based on a multi-disciplinary project on antimony therapy, in which we explored some of these factors in two different epidemiological settings: anthroponotic visceral leishmaniasis (VL, Nepal) and zoonotic cutaneous leishmaniasis (CL, Peru). Average treatment failure rate was 11.4% in Nepal and 23.9% in Peru, and it was associated with a series of risk factors, differing according to the type of disease. By in vitro susceptibility testing, we found SbV-resistant strains among the 6 species endemic in the respective study areas, but surprisingly, a large proportion of them were isolated from patients responding well to treatment (in both epidemiological settings). Two different resistance phenotypes were encountered in vitro, some strains are resistant to SbV and SbIII (the reduced and active drug), while others are only resistant to SbV; suggesting resistance to 1 particular drug can be a pleiomorphic story in Leishmania. This hypothesis is supported by two observations: (i) several molecular signatures for resistance were identified, but varied cross species, and even between different genetic groups of the same species and (ii) a population genetics approach revealed a polyclonal structure among resistant parasites. Lessons from this study are discussed in the context of control programmes.