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Tropical Diseases Conference 2019: Characterization of new therapeutic drugs against leishmaniasis - Ana Poveda - Central University of Ecuador, South America

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Leishmaniasis is a largely neglected infection caused by Leishmania spp. parasites. The first-line treatment, antimonate meglumine, has a large number of adverse effects, high costs and is developing resistance. New alternatives are mandatory. Here we show the results obtained with synthetic compounds (bis(spiropyrazolone)cyclopropanes, Schiff bases) and well knownold antibiotics used against bacteria1. These compounds were chosen because many evidences indicate that bis(spiropyrazolone)cyclopropanes and Schiff bases have biological properties. The antibiotic selected was the fluoroquinolones (FQ), a drug largely used against bacteria2. FQ are a good candidate since sequence alignments shows a good conservation of topoisomerases type II, the molecular target. To determine the leishmanicidal effect of drugs, a fluorescence method was optimized to determine MIC and IC50 in cultures of L. mexicana and L. braziliensis promastigotes3. In order to determine the toxicity and presence of DNA damage, bioassays with yeast were implemented (drop test using yeast mutants and comet assay). However, many compounds has a limited solubility. This limitation could be solved loading it into liposomal systems such as the transferosomes, ultradeformable nanovesicles4. Transferosomes were characterized in terms of size, polydispersity index, zeta potential, entrapment percentage, dissolution profile and physical stability. These nanovehicles enhanced the leishmanicidal activity compared with enrofloxacin in solution, around 15 times. So the nanoencapsulation could be an interesting approach to develop a topic formulation to treat cutaneous leishmaniasis. Our results indicate that two Schiff bases, one bis(spiropyrazolone)spirocyclopropane and one FQ, are potential candidates for alternative treatment of leishmaniasis. Next efforts are oriented to assay these drugs in murine models.

Leishmaniasis is a disease caused by Leishmania-type parasites. This is transmitted by the bite of certain kinds of sandflies. There are three main forms the disease can present: cutaneous, mucocutaneous, or visceral. The cutaneous shape presents ulcers of the eyes, while the mucocutaneous shape presents ulcers of the face , mouth, and nose, and the visceral shape begins with skin ulcers and eventually presents fever, low red blood cells, and spleen and liver enlargements. More than 20 species of Leishmania cause infections in humans. Poverty, poverty, deforestation and urbanisation are risk factors. These three forms can be identified by microscopic examination of the parasites. Furthermore, blood tests can diagnose visceral disease. Leishmaniasis can be avoided in part by sleeping under insecticide-treated beds. Certain steps include applying insecticides to kill sandflies, and early treatment to avoid further spread of the disease to humans. The treatment needed is determined by where the disease, the Leishmania species, and the type of infection is acquired. Some potential visceral disease drugs include liposomal amphotericin B, a mixture of pentavalent antimonials and paromomomycin, and miltefosine. Paromomomycin, fluconazole, or pentamidine may be useful for cutaneous illness. Leishmaniasis can be avoided in part by sleeping under insecticide-treated beds. Certain steps include applying insecticides to kill sandflies, and early treatment to avoid further spread of the disease to humans. The treatment needed is determined by where the disease, the Leishmania species, and the type of infection is acquired. The leishmaniasis is diagnosed by direct visualization of the amastigotes (Leishman – Donovan bodies) in the hematology laboratory. Buffy-coat preparations of peripheral blood or marrow aspirates, spleen , lymph nodes or skin lesions should be distributed over a slide to create a thin smear and stained for 20 minutes with Leishman stain or Giemsa stain (pH 7.2). Amastigotes are seen in blood and spleen monocytes, or, less generally, in circulating neutrophils and macrophages of aspirated tissue. They are 2–4 μm in diameter, thin, round bodies with an indistinct cytoplasm, a nucleus, and a thin, rod-shaped kinetoplast. Amastigotes can

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sometimes be seen lying free between cells. The recovery of tissue samples is nevertheless also painful for the patient. Other indirect immunological diagnostic methods, including enzyme-linked immunosorbent assay, antigen-coated dipsticks, and direct agglutination test are thus created. While these tests are readily available, because of their inadequate sensitivity and accuracy they are not the traditional diagnostic tests. The diagnosis is determined by where the illness, the Leishmania species and the type of infection is acquired. Liposomal amphotericin B is the approved treatment for visceral leishmaniasis in India , South America and the Mediterranean, and is also used as a single dose. The evidence surrounding skin leishmaniasis care is low. For cutaneous leishmaniasis a variety of topical therapies can be used. Increasing therapies are successful depends on the pressure, with L being affected with topical paromomycin. Dur, L. Truffle, L. Mexico, L. Panamensis, L. Braziliansis of this. There are several different polymerase chain reaction (PCR) tests available to diagnose Leishmania DNA. Essentially a precise and reliable diagnostic technique is possible for this assay. Minicircle kinetoplast DNA present in parasite is used for the most active PCR studies. Kinetoplast DNA includes maxicircle sequences for mitochondrial proteins (~25-50 per parasite), and directs kinetoplast RNA in its minicircles (~10'000 per parasite). Using this particular process, even with a very low parasite charge, one can still detect Leishmania. Other PCR approaches have been superior when diagnosing a particular species of Leishmania, as opposed to identification only. The diagnosis is determined by where the illness, the Leishmania species and the type of infection is acquired. Liposomal amphotericin B is the approved treatment for visceral leishmaniasis in India , South America and the Mediterranean, and is also used as a single dose. Cure levels were registered at a single dose of amphotericin at 95 percent. Fast all infections in India are immune to pentavalent antimonials. In Africa it is suggested to have a mixture of pentavalent antimonials and paromomycin. Although these may have significant side effects. Miltefosine is mainly used in the treatment of visceral and New World cutaneous leishmaniasis, and clinical trials are ongoing in many countries for this use. The drug is now classified under the WHO Model List of Essential Medicines as a key medicine for treating leishmaniasis. Some medicinal agents have some effectiveness against visceral or cutaneous leishmaniasis, but a 2005 study found that the only effective oral treatment for all types of leishmaniasis is miltefosine.

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