Abstract BSP – oral presentation
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The development of an oral oleylphosphocholine treatment for cutaneous leishmaniasis

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Introduction

With an estimated 0.7 to 1 million new infections a year globally, cutaneous leishmaniasis (CL) is the most prevalent form of leishmaniasis; it clinically manifests as a variety of skin lesions ranging from closed nodules, to plaques and ulcers. Currently recommended drugs have proved to be clinically unsatisfactory indicating the urgent need for novel safe and efficacious drugs.

Oleylphosphocholine, an alkylphoshoplipid structurally similar to miltefosine, demonstrated potent activity against *Leishmania* species causing visceral leishmaniasis (VL) both *in vitro* and *in vivo*. Given the discrepancies between the target product profiles of VL and CL, we here report the *in vitro* and *in vivo* efficacy of orally administered oleylphosphocholine-based formulations (two with a fast-release and two with a slow release profile) against CL-causing *Leishmania* species.

Materials and methods

The antileishmanial activities of OLPC and miltefosine were evaluated against intracellular amastigotes of six *Leishmania* species (*L. major*, *L. tropica*, *L. aethiopica*, *L. mexicana*, *L. braziliensis*, *L. panamensis*). Following promising results, the *in vivo* efficacies of both drugs were investigated in two stages. First, the performance of the efficacious dose for OLPC for VL was evaluated using an experimental CL model. Secondly, the antileishmanial activity of various formulations of OLPC with diverse release profiles was investigated alongside a dose response using bioluminescent *L. major* parasites. Tissue concentrations in skin of OLPC were determined using LC-MS/MS.

Results and discussion

The *in vitro* activities of OLPC against CL-causing species ranged from 0.74 to 31.06 uM and are similar to those obtained for miltefosine. In the experimental CL models, OLPC administered orally at a dose of 35 mg/kg once daily for ten days was able to significantly reduce the lesion size to a similar extend as the positive control (paromomycin sulphate, ip, 50 mg/kg/day – repeated-measures ANOVA, post-hoc Tukey, $p < 0.05$). In contrast, the administration of miltefosine (same dose and regimen as OLPC) only resulted in a halt of the lesion size progression but was unable to decrease the lesion diameter. The second *in vivo* study was able to confirm these results and demonstrated a superior activity of the fast- (OLPC with lactose or cellulose carrier) over the slow-release (OLPC absorbed into a diffusion-controlled silica carrier) test formulations as measured by a significantly greater bioluminescence signal (~ parasite load) decrease when compared to the untreated controls.

Extraction of the drugs from the infected skin site 24 hours after the oral administration of 1 dose (35 mg/kg) demonstrated higher concentrations of OLPC versus miltefosine (t-test). This difference was no longer present at the end of the 10-day treatment period even though OLPC blood concentrations at the end of treatment were 2-fold higher than for miltefosine.

Conclusions

OLPC demonstrated potent activity in the intracellular macrophage model using a range of CL-causing species and was able to reduce the parasite load in an experimental *L. major* CL model after ten days of treatment. In a next step, the drug delivery profile into *Leishmania*-infected and uninfected mouse skin will be compared using skin microdialysis.

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