

Macrophages as Therapeutic Targets During Visceral Leishmaniasis

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Problem: Visceral leishmaniasis (VL) is caused by obligate intracellular protozoan parasites that exhibit tropism for reticuloendothelial macrophages, causing a severe and potentially fatal disease. Although *Leishmania* species can parasitize several different mammalian cell types, the definitive host cell and site of parasite replication is the tissue macrophage. This represents a particular challenge to the host since macrophages are also the cell type ultimately responsible for killing parasites under ideal immune conditions.

Hypothesis: We hypothesize that selectively depleting macrophages in VL-infected mice will aid in the resolution of disease.

Methods: Susceptible BALB/c mice were used for all studies. Mice were treated with clodronate liposomes at varying timepoints prior to or post-VL infection to deplete macrophages. Controls received PBS liposomes. Drug comparison studies included sodium stibogluconate, no treatment, and dual treatment groups. At varying timepoints post-treatment livers and spleens were collected to quantify parasite burdens and assess tissue histopathology.

Results: Mice treated with clodronate exhibited markedly reduced parasite burdens. In addition, mice that were treated with clodronate both prior to infection and one day post-infection showed little or no immunopathology compared with PBS controls. It was further found that liposomal clodronate was as efficacious as sodium stibogluconate, the standard-of-care therapeutic during clinical infections, in controlling experimental VL.

Conclusion: This research may serve as a foundation in determining whether macrophage-selective drugs represent viable treatment options for human diseases that chronically infect host cell macrophages, such as leishmaniasis and tuberculosis.