International Immunopharmacology 70 (2019) 324–337

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Doxycycline hyclate: A schistosomicidal agent *in vitro* with immunomodulatory potential on granulomatous inflammation *in vivo*

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ARTICLE INFO

Keywords:
Antiparasitic chemotherapy
Experimental pathology
Parasitology
Schistosomiasis

ABSTRACT

We investigated the effect *in vitro* and *in vivo* of doxycycline hyclate (Dx), a broad-spectrum antibiotic inhibitor of matrix metaloproteinases (MMPs), on adult *Schistosoma mansoni* worms and granulomatous liver inflammation in infected mice. Adult *S. mansoni* worms in culture treated with different concentrations of Dx (50–180 μg/mL) were studied for eight days to assess its morphology, eggs production, and mortality. Uninfected mice and those infected with *S. mansoni*, untreated and treated with praziquantel (Pz; 200 mg/kg) or Dx (50 mg/kg), were evaluated for 60 days. Our results indicated that Dx induced dose-dependent integumentary lesions (bubbles, tubercle collapse, spicule disappearance, peeling, and erosion), reduced mating rate and eggs-laying in adult *S. mansoni* worms. The effective lethal dose required to kill 50% of worms was 112.0 μg/mL Dx (DL_{50}). In mice, *S. mansoni* infection induced hepatomegaly, intense IL-4, IL-10, TNF-α and TGF-β production, granulomatous inflammation and hepatic glycogen depletion. The number and size of the granulomas was similar in untreated and Dx-treated animals. Untreated animals showed a predominance of productive granulomas, and intense MMP-2 and MMP-9 activities. Dx-treated mice exhibited a significant increase in IL-4 levels, tissue inflammation, proportion of involutive granulomas, and hepatic collagenogenesis, as well as attenuated MMP-2 and MMP-9 activities. Our findings indicated that Dx is toxic to adult *S. mansoni* worms *in vitro*. However, *in vitro* beneficial effects were not reproduced *in vivo*, since Dx treatment increased liver granulomatous inflammation and collagenogenesis in *S. mansoni*-infected mice by a process potentially associated with Dx-mediated hepatic MMP-2 and MMP-9 inhibition.

1. Introduction

Schistosomiasis is a disease caused by trematodes of the genus Schistosoma [1,2]. Considering all *Schistosoma* species, about 240 million people in 78 countries are infected and 800 million people live in areas endemic to the disease. In the world, the highest incidence and prevalence of schistosomiasis occurs in regions of the Middle East, South America, Southwest Asia and especially Africa [3,4]. The species responsible for schistosomiasis in Brazil is *Schistosoma mansoni*, which causes a chronic and debilitating disease [4]. In this country, about 25 million people live in an area with a risk of schistosomiasis and approximately 2.5 to 6 million individuals are infected, especially in poor and rural areas where sanitation and quality of life are precarious [5,6].

The life cycle of *S. mansoni* is heteroxenic, passing one phase in the mollusk, the intermediate host, and another phase in humans, the definitive hosts [7,8]. Schistosomiasis develops in humans in acute and chronic phases [9]. The acute phase is generally asymptomatic and represents a mild form with hepatointestinal involvement. The chronic phase, when symptomatic, manifests as hepatosplenomegaly and portal hypertension and is recognized as an advanced hepatosplenic form [10]. Acute schistosomiasis is characterized by the presence of numerous periovular granulomas in multiple organs, especially in the liver, intestines and lungs [10]. These granulomas are large, with a predominantly exudative component rich in eosinophils, poorly

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https://doi.org/10.1016/j.intimp.2019.02.032
Received 29 January 2019; Received in revised form 13 February 2019; Accepted 19 February 2019