DIC, a New 4,5-dihydroisoxazole Derivative, as a Potential Compound to Modulate the Schistosomal Granuloma Formation and Liver Fibrosis

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INTRODUCTION. Schistosomiasis is a chronic disease caused by Schistosoma. The disease remains a major, neglected, poverty-related health problem in many tropical areas. The pathology associated with schistosomiasis is attributed to the granulomatous inflammations and subsequent fibrosis induced by parasite eggs that become trapped in the liver. Considering that the potent inflammatory response in granuloma is mediated by pro-inflammatory cytokines, the use of drugs that act by modulating the inflammatory response could offer an alternative strategic to the treatment of schistosomiasis. The compound 3-(3-chloro-phenyl)-5-(4-pyridyl)-4,5-dihydroisoxazole (DIC) is a five-membered heterocyclic compound with broad anti-inflammatory activity, in particular, acts by inhibiting the release of High Mobility Group Box-1 (HMGB1) proteins. The increase of HMGB1 serum levels occupies a central role in the pathogenesis of inflammatory chronic diseases. Thus, in this work we investigated the effect of DIC in mice with schistosomiasis and also analyzed the role of HMGB1 as an inflammatory mediator in schistosomiasis.

MATERIAL AND METHODS: The cytokines levels were determined by CBA. Liver sections were stained with HE and picro-sirius for granuloma size and collagen analysis respectively.

RESULTS AND DISCUSSION. The treatment with DIC (10 mg/kg/day) not only decreased cellular infiltration around the eggs deposited in the liver, but also reduced the granuloma collagen, likely by the drastic declined of IL-13 levels in the serum. Cytokines as INF-γ, IL-10, IL-6, IL-5, IL-4 and IL-17 have its levels decreased in mice with schistosomiasis and treated with DIC. Importantly, we found for the first time that HMGB1 serum levels are increased in human with chronic schistosomiasis. Our data also suggest that the levels of HMGB1 are increased in mice and DIC contribute for its downmodulation. CONCLUSIONS. The compound DIC seems to be an important modulator of liver fibrosis and can therefore, be thought as a promising drug to use concomitantly with praziquantel as an alternative for the treatment of schistosomiasis.

Keywords: 4,5-dihydroisoxazol, schistosomal granuloma, liver fibrosis

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