A New 4,5-dihydroisoxazol Derivative as a Potential Therapeutic agent for Schistosome Egg Granuloma Formation

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Schistosomiasis is a helminthic disease, in which the main immunopathology consists of a granulomatous and fibrosing reaction against parasite eggs. Granuloma formation is controlled and modulated by Th1 cytokines like TNF-α. TNF-α plays a central role in circuoval granuloma formation. In this regard, infected mice that were treated with monoclonal antibody against TNF-α revealed a significant decrease of the granuloma area. Thus, inhibition of cytokine activities could offer an attractive therapeutic alternative for chronic schistosomiasis. DIC, a new 4,5-dihydroisoxasole derivate has been shown to regulate NF-kB/MAPK pathways, by decreasing the release of TNF-α and IL-6. Moreover, this compound appears to inhibit the secretion of HMGB1 from macrophages stimulated with LPS. HMGB1 is a highly conserved nuclear protein that can be secreted by innate immune cells in response to pathogenic products, playing a central role in the pathogenesis of various inflammatory disorders. Thus, in the present study we evaluated the role of DIC in the immunomodulation of granulomatous inflammation and liver pathology. We also studied the influence of HMGB1 in acute schistosomiasis. Mice were infected with 80 Schistosoma mansoni cercariaes and treated with DIC at a dose of 5 mg/kg body weight per day by 35 days. DIC was effective in reducing hepatic granuloma area and liver collagen content by 31%. In addition, western blot and immunohistochemistry analysis of the liver of mice treated with DIC resulted in a decrease in the levels of HMGB1. Importantly, we observed high levels of HMGB1 surrounding the hepatic granuloma in non-treated infected mice.

KEYWORDS: schistosomiasis, inflammation, HMGB1, 4,5-dihydroisoxasole, anti-cytokine agents.

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