

PRELIMINARY RESULTS OF THE EFFECTS OF PENTOXIFYLLINE THERAPY IN THE MURINE MODEL OF PARACOCIDIOIDOMYCOSIS

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Pentoxifylline (PTX) was found to be an inhibitor of the proinflammatory cytokine tumor necrosis factor (TNF)- α . In murine paracoccidiodomycosis (PCM), TNF- α is considered a determinant factor in resistance to *Paracoccidoides brasiliensis* (Pb). Few hours after i.p. Pb inoculation, TNF- α levels are higher in susceptible than in resistant mice. Released by macrophages, TNF- α is required for this cell accumulation and differentiation into epithelioid cells and for the persistence of well-formed PCM granulomas. Interferon (IFN)- γ can activate infected macrophages to secrete TNF- α , inhibiting the replication of Pb. The effects of PTX therapy were tested in B10.A mice, susceptible to PCM, using as parameters the dissemination of viable fungi to various organs, demonstrated by colony-forming units (CFU) assays, and the development of specific cellular immune responses against Pb antigen, demonstrated by delayed-type hypersensitivity (DTH) reactions. PTX therapy, in dosages of 30 or 50mgPTX/kg/day, was given in drinking water and began 24 hours after Pb i.p. inoculation. Two days after infection, the number of CFU/gram of tissue (CFU/g) in the lungs of mice treated with 30mgPTX/kg/day was diminished when compared with both untreated or 50mgPTX/kg/day treated mice. In the 7th day, both 30 or 50mgPTX/kg/day treated mice showed lower CFU/g in the epiplooa. On the 15th and the 30th day after infection, no difference was found in CFU/g between untreated or 50mgPTX/kg/day treated mice. However, on the 15th day, the number of CFU/100 μ L of organ suspension was lower in the liver of 50mgPTX/kg/day treated mice, while in the 30th day, CFU/100 μ L of liver was higher in mice submitted to this therapy. In DTH reactions, both untreated and 50mgPTX/kg/day treated mice showed a profile in keeping with that described for the susceptibility pattern, characterized by early and ephemeral responses. The animals presented, at the 7th day post-infection, low DTH responses, that increased slightly in the 15th day. It has been reported that the inhibition of TNF- α in murine PCM, either by the use of anti-TNF- α antibodies or by the knock-out of the p55 TNF- α receptor gene, lead to an increase in disease severity and in the mortality rates specially after the 2nd week of infection, confirming the protective role of TNF- α . In our assays, this increase only appears at the 1st month. However, the events occurring at the 2nd day of infection suggest that in a very early phase of PCM TNF- α might have a non-protective role, once its inhibition reduced the fungal load isolated from the lungs of mice. This phenomenon probably is accompanied by alterations in the cytokine profile, that must be investigated in a more deep way.