ORT_06 - Thiourea Derivatives with Antimycobacterial and Anti-Inflammatory Activity as an Adjuvant Treatment Strategy for Severe Pulmonary Tuberculosis

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**Introduction:** The increase in the incidence of M. tuberculosis resistant strains and hypervirulence is a major threat to public health and encourages the search for new anti-TB drugs. Adjunctive approaches, such as the use of anti-inflammatories in addition to antibiotic treatment, have been encouraged for the treatment of severe cases of TB. New substances with dual action, antimycobacterial and anti-inflammatory, represent a promising therapeutic tool.

**Objectives:** To evaluate the potential of forty-six thiourea derivatives regarding their antimycobacterial and anti-inflammatory activity as an adjuvant treatment strategy for severe pulmonary TB.

**Methodology:** Derivatives of thioureas were evaluated against the culture of Mtb H37Rv and M299 for their potential to inhibit growth, and in cell culture of RAW 264.7 macrophages for their ability to inhibit inflammatory mediators (NO and TNF-α) and cytotoxicity. The most active thioureas for both activities were evaluated for their inhibitory action on intracellular mycobacterial growth in RAW 264.7 macrophages infected by Mtb H37Rv through CFU counting. Derivatives 28 and 29 were evaluated in the murine model of severe pulmonary TB induced in C57Bl/6 mice by a hypervirulent Mtb strain.

**Results:** Forty-six thiourea derivatives were synthesized and screened for anti-inflammatory action, cytotoxicity and antimycobacterial activity. Derivatives of thioureas 10, 15, 16, 28 and 29 showed dual activity being able to inhibit the production of NO, TNF-α, IL-1β, with emphasis on derivative 28 for IL-1β, and 29 for TNF-α. These derivatives were also capable of inhibiting the growth of laboratory and hypervirulent Mtb strains in vitro. Derivatives 28 and 29 with greater potential for both activities (anti-inflammatory and antimycobacterial) were evaluated for their therapeutic effect in the treatment of severe induced TB in C57Bl/6 mice by hypervirulent Mtb strain. Treatment with derivatives 28 and 29 for 2 or 3 weeks was able to decrease the area of granulomatous pulmonary pathology and reduce the development of necrotic areas. Accordingly, the treatment showed a significant reduction in the frequency of leukocytes in the lung, especially neutrophils, and decreased the production of inflammatory cytokines quantified in the supernatant of the ex vivo culture of lung cells and inhibition of bacillary growth in the lungs.

**Conclusion:** Thiourea derivatives 28 and 29 are promising for prospective studies aimed at generating new anti-TB drugs for the adjuvant treatment of severe TB associated with exacerbated inflammation.

**Keywords:** tuberculosis, treatment, inflammation