Effects of a new selective inhibitor of PARPs in asthma-like reaction and bleomycin-induced lung fibrosis animal models

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Poly(ADP-ribose)polymerases (PARPs) are NAD dependent enzymes, involved in the maintenance of genomic integrity, epigenetic regulation of gene expression, control of cell cycle and cell death. PARPs play an important role in tissue injury in association with oxidative stress and inflammation. Activation of PARPs is considered a key event in the molecular and cellular processes leading from acute asthma attacks to bronchial hyper-reactivity, leukocyte recruitment, chronic inflammation, remodeling and lung damage. PARP-1, the most abundant of these enzymes, has been known to contribute to asthmatic airway inflammation and it is involved in allergen-induced bronchoconstriction (Suzuki et al., 2006).

Here we studied the effects of hydroxyl-dimethylaminomethyl-thieno[2,3-c]isoquinolin-5(4H)-one (HYDAMTIQ), a selective PARP-1and PARP-2 inhibitor, in *in vivo* models of asthma-like reaction in guinea pigs and bleomicin-induced lung fibrosis in mice.

Ovalbumin(OA)-sensitized guinea pigs, treated i.p. for 7 days with HYDAMTIQ (1, 3 and 10 mg/kg b.wt) or saline were challenged with OA (5mg/ml) for 60 sec and respiratory parameters were recorded. After 48 h the animals were anesthetized and challenged with MeCh (0.1 mg/ml) for 60 sec. Changes in the pressure at the airway opening (PAO) were registered. At the end, bronchoalveolar lavage (BAL) fluid was collected for PAR expression, and lungs were removed for the evaluation of eosinophil infiltration, mast cell degranulation, oxidative stress marker activation, prostanoid and cytokine production.

C57/bl6 mice, treated with bleomicin (0.05UI), received for 21 days HYDAMTIQ (1, 3 and 10 mg/kg b.wt) or saline. PAO was assayed and lung tissue was processed to evaluate the production of oxidative stress, inflammatory and fibrotic markers as well as percentage of positive goblet cells and thickness of smooth-muscle layer.

Our results indicate that in the guinea pig model, HYDAMTIQ exerts an anti-inflammatory effect in a dose-related way, as shown by the significant decrease of prostaglandin (PGD_2) and inflammatory cytokine (TNFα, IL-1β, IL-5, and IL-18) production, eosinophil infiltration, goblet cell number, thickness of smooth muscle layer, and collagen deposition. These effects are accompanied by a decrease of PAO, mast cell degranulation and histamine release. Moreover, HYDAMTIQ significantly reduces parylated protein content both in lung tissues and in BAL cells of guinea pigs sensitized and challenged with OA.

In lung fibrosis model, HYDAMTIQ exerts an anti-fibrotic effect, as shown by the significant decrease of pro-fibrotic cytokine TGF-β level and inflammatory cytokines (TNFα, IL-1β) production. Moreover, it reduces collagen deposition, goblet cell number and PAO.

The present findings suggest that HYDAMTIQ could be a promising approach to alleviate lung inflammatory and fibrotic diseases and could provide background for future clinical trials to evaluate the possible anti-asmathic and anti-fibrotic potential of PARP inhibitors.

Suzuki Y et al. (2004). J Pharmacol Exp Ther. 311:1241-1248.