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Cationic salt dry powders inhibit inflammatory responses in a rhinovirus-induced exacerbation mouse model of allergic airway inflammation

P.L. Wright, S. Kong, T. Brogan, S. Arold, P. Okerholm, F. Saia, R.W. Clarke, D.L. Hava

RATIONALE: Rhinovirus (Rv) infection is highly associated with respiratory disease acute exacerbations (AE). AEs drive disease progression and cause loss of lung function, yet no current therapies target this infectious component. Cationic salt based dry powder (DP) formulations were developed as host-targeted therapies that broadly reduce viral infection *in vitro*, including Rv infection of normal human bronchial epithelial cells (NHBE). The efficacy of a lead cationic salt DP (PUR118) was tested in an Rv mouse model of infection and AE using Rv1B, a minor strain Rv and naïve or ovalbumin (OVA)-challenged mice (Bartlett NW et al Nat Med 2008). METHODS: Naïve mice were treated with PUR118 or a DP control by a whole body exposure system 1 h before and 4 h after intranasal infection with RV1B ($5x10^6$ $TCID_{50}$). Bronchoalveolar lavage (BAL) inflammation was assessed 24 h post-infection. A similar dosing regimen was used for the AE model where OVA challenged mice received BID treatments on days of OVA challenge (Day 27, 28 and 29) at 1 h before and 4 h after challenge with 1% aerosolized OVA. On the final day of challenge, mice were infected with Rv1B 1h post OVA exposure to induce an AE-like response. RESULTS: Rv1B infection caused significant neutrophilic inflammation in naïve mice ($7.5x10^5$ BAL neutrophils/ml) and exacerbated inflammation in OVA challenged mice (44% over control) with increased neutrophils and corresponding cytokines and chemokines. In both naïve and Rv1B AE mice, PUR118 treatment inhibited neutrophilic inflammation by 38% and 40%, respectively. Reductions in neutrophils correlated with reduced levels of chemokine expression including KC, MIP1α and MIP2, which are all important for neutrophil chemotaxis. Furthermore, lung histology was greatly improved in mice treated with PUR118 as evidenced with reduced bronchiolar and vascular cellular infiltrate. CONCLUSIONS: Together, these data show cationic salt DP treatment not only inhibits Rv infection of airway epithelium *in vitro*, but greatly diminishes Rv-induced airway inflammation and AE responses in a Rv-driven asthma-like mouse model. Since inflammatory responses resulting from AEs are a leading cause of increased incidence of future AEs, there is great need for therapies that target AE-associated inflammation. The anti-inflammatory activity of PUR118 along with its broad spectrum approach, which is distinct from current therapies, makes it an ideal therapy for the prevention of AEs in patients with respiratory disease.