

88 Levofloxacin pharmacokinetics (PK) after administration of MP-376 (Levofloxacin inhalation solution; Aeroquin) in children with cystic fibrosis (CF)

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Introduction: MP-376 is a proprietary formulation of levofloxacin (LVX) for aerosol administration. We characterized LVX serum and sputum exposures in children with CF receiving MP-376.

Methods: Medically stable patients with CF aged 6–16 years (FEV1 range 37 to 127% of predicted) were enrolled. Patients received single daily doses of MP-376 of either 180 (n=7) or 240 mg (n=20) for 14 days via a customized eFlow nebulizer based on body weight of 22–29 kg and ≥ 30 kg, respectively. Repeated serum and sputum samples were collected for LVX concentration on Days 1 and 14. PK analyses were conducted using non-compartmental methods.

Results: 25 patients had evaluable data to estimate serum PK parameters on at least one occasion (22 from both days, 3 from Day 1 only). Mean serum AUC (CV%) was 8.1 (77.1) and 9.8 (55.7) mg*h/L and mean serum Cmax (CV%) was 1.2 (81.2) and 1.5 (62.8) mg/L for 180 and 240 mg doses, respectively. Sputum Cmax was highly variable and the mean (CV%) for both doses combined was 3120 (188) mg/L on Day 1 (n=13). There was no apparent association between total body weight and/or age with LVX serum or sputum exposure.

Conclusions: Serum and sputum LVX levels in pediatric CF patients are comparable to those observed following aerosol MP-376 in adult CF patients. Based on these data, children 6 years of age and older and weighing at least 30 kg should receive the same dose as adult CF patients.

90 Inhibitory effects of RV1088, a novel narrow spectrum kinase inhibitor, on RSV infection in primary bronchial epithelial cells obtained from patients with cystic fibrosis

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Objectives: Respiratory syncytial virus (RSV) is a leading cause of serious lower respiratory infections in patients with respiratory disorders such as cystic fibrosis; however, there are no viable treatments available. The aim of this study is to evaluate the effects of RV1088, a narrow spectrum kinase inhibitors (NSKI), on RSV infection in human bronchial epithelial cells from healthy volunteers (NHBE) and patients with cystic fibrosis (CF-BEC) and Hep2 cells.

Methods: RSV A2 strain was infected to Hep2, NHBE and CF-BEC at 0.001MOI for 1 hr and then non-infected virus was washed out. The plates were further incubated for 4 days and RSV infection was assessed by ELISA targeting RSV fusion (F) protein.

Results: RSV infected all three cell types but CF-and NHBE showed greater infection than Hep2 cells. RV1088, fluticasone propionate (FP), a corticosteroid, and Ribavirin were added 2hrs before and 1 hr after infection. FP (0.04 ug/ml or 0.2 ug/ml) did not inhibit RSV infection in any cell type. Ribavirin (10 ug/ml) inhibited RSV-F protein expression by 93% in Hep2 cells, but the maximum inhibitory effects were reduced in primary cells (78% in HBEC, 53% in CF-BEC). In contrast, although RV1088 inhibited RSV load by only 58% at maximum in Hep2, RV1088 showed superior effects in both NHBE (IC₅₀ value of 22 nM and E-max of 87%) and in CF-BEC (IC₅₀ value of 58 nM and E-max of 78%). At the concentrations used, no effects on cell viability were detected.

Conclusion: RV1088 is a novel compound which inhibits RSV replication by targeting host cell signaling, suggesting that RV1088 could be an important new therapy for cystic fibrosis especially RSV-induced exacerbation.

89 Superior effects of RV568, a narrow spectrum kinase inhibitor, on RSV infection in primary bronchial epithelial cells obtained from patients with cystic fibrosis

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Objectives: Respiratory syncytial virus (RSV) is a leading cause of serious lower respiratory infections in patients with respiratory disorders such as cystic fibrosis; however, there are no viable treatments available. The aim of this study is to evaluate the effects of RV568, a narrow spectrum kinase inhibitor (NSKI), on RSV infection in human bronchial epithelial cells from healthy volunteers (NHBE) and patients with cystic fibrosis (CF-BEC) and Hep2 cells.

Methods: RSV A2 strain was infected to Hep2, NHBE and CF-BEC at 0.001MOI for 1 hr and then non-infected virus was washed out. The plates were further incubated for 4 days and RSV infection was assessed by ELISA targeting RSV fusion (F) protein.

Results: RSV infected all three cell types but CF-and NHBE showed greater infection than Hep2 cells. RV568, fluticasone propionate (FP), a corticosteroid, and Ribavirin were added 2hrs before and 1 hr after infection. FP (0.04 ug/ml or 0.2 ug/ml) did not inhibit RSV infection in any cell type. Ribavirin (10 ug/ml) inhibited RSV-F protein expression by 93% in Hep2 cells, but the maximum inhibitory effects were reduced in primary cells (78% in HBEC, 53% in CF-BEC). In contrast, although RV568 inhibited RSV load by only 24% in Hep2, it showed superior effects in NHBE (IC₅₀ values of 41 nM and E-max of 51%), and the efficacy was improved in CF-BEC (IC₅₀ value of 69 nM and E-max of 84%). At the concentrations used, no effects on cell viability were detected.

Conclusions: RV568 is a novel compound which inhibits RSV replication by targeting host cell signaling, suggesting that RV568 could be an important new therapy for cystic fibrosis especially RSV-induced exacerbation.

91 Medical rationale for nebulisation of a novel high-concentration (100 mg/mL) aqueous azithromycin inhalation solution

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Objective: In addition to its antibiotic activity, Azithromycin (AZM) has anti-inflammatory, immunomodulatory and mucus regulating effects. Since oral bioavailability is only about 37%, inhalation can provide high local doses in the airways as the target site to treat CF and bronchiectasis (BE). Topical use of aerosolized azithromycin may increase mucociliary clearance, decrease mucus hypersecretion and reduce IL8, neutrophils, rhinovirus replication, pro-inflammatory proteins, nasal polyps, and protect ciliated epithelium against oxidative damage. Hence, based on such literature data local effects of AZM may improve therapeutic efficacy over oral or i.v. application reducing at the same adverse side effects and resistance formation as known from other inhaled antibiotics.

Results: Drug delivery efficiency of a novel taste masked AZM solution (100 mg/mL) utilizing a customised eFlow electronic nebuliser was assessed by breath simulation tests carried out in triplicate, each. In-vitro delivered doses (DDs) of ~75% and respirable dose (RD) of ~50% suggest that a lung deposition of about 40% can be expected. Inhalation tests confirmed good tolerability and acceptable taste.

Conclusion: Targeted aerosolized AZM therapy by nebulisation via eFlow technology platform devices may be more advantageous and effective compared to oral application. Hence, the proposed targeted delivery concept of a novel AZM inhalation formulation may open new perspectives for the treatment of CF and BE as well as severe neutrophilic asthma, COPD and mycobacterium avium complex induced infections. Thus, clinical studies are warranted to evaluate the therapeutic value of inhaled Azithromycin.