Effects of Corticosteroid in the Rat Ovalbumin Pulmonary Inflammation Model

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1 INTRODUCTION

The Brown Norway Rat lung inflammation model is an established allergen dependent pharmacokinetic/pharmacodynamic (PK/PD) model that can be used to investigate the basic pathology of disease and to assess the in vivo efficacy of anti-asthma drugs.

2 MATERIALS AND METHODS

Rats (N=8) were assigned to naive or to ovalbumin (OVA) sensitized groups. The OVA animals were further assigned to vehicle or corticosteroid treatment. Rats were treated with betamethasone (0.003 to 3mg/kg, PO), dexamethasone (0.003 to 3mg/kg, PO) or budesonide (3mg/kg, PO). Two weeks following sensitization, animals were challenged with an aerosol of OVA by whole-body inhalation. Lungs were lavaged 6 to 48 hours after challenge and Broncho Alveolar Lavage Fluid (BALF) assessed for differential cell counts and inflammatory mediators (IFN, IL-1, IL-4, IL-5, IL-6, IL-10, IL-13, KC/GRO and TNF, MSD multiplex platform).

3 RESULTS

Significant increases in neutrophils (30 fold from 6 to 24 hours) and eosinophils (7 to 10 fold at 48 hours) were observed in the BALF of OVA challenged animals compared to control animals. Betamethasone and dexamethasone dose-dependently inhibited neutrophils (up to 100%) and eosinophils (up to 92%). Budesonide reduced neutrophils by 71% and eosinophils by 91%. Following OVA challenge, increases (up to 6 fold) in all mediators were seen in the BALF apart from KC/GRO (no increase), and TNF (80-fold increase). Dexamethasone at 3mg/kg decreased the cytokines levels in the BALF samples and were generally comparable to non-OVA levels.

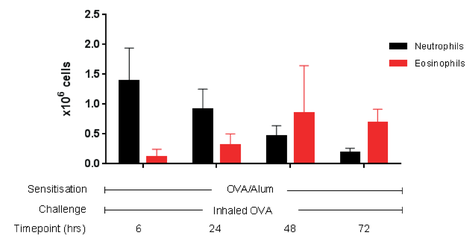

Figure 1: Neutrophils and Eosinophils Timecourse Following Ovalbumin Exposure

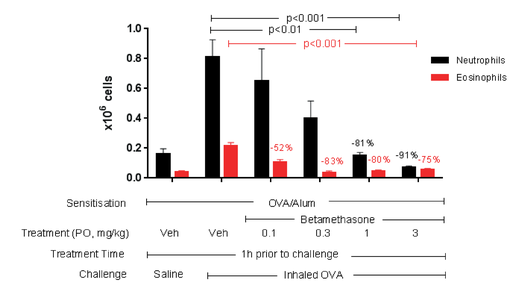

Figure 2: Betamethasone Dose Response

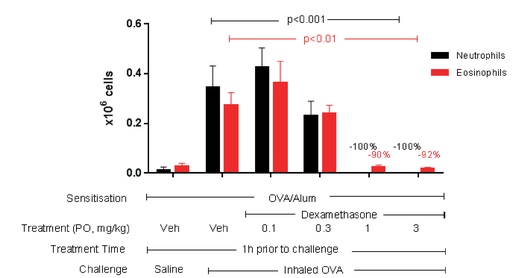

Figure 3: Dexamethasone Dose Response

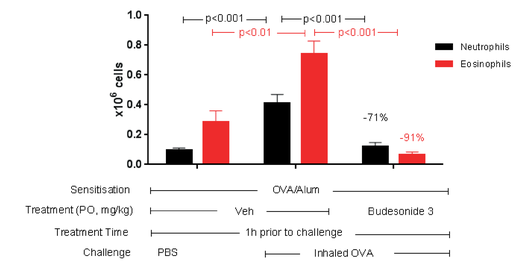

Figure 4: Budesonide Dose Response

Table 1: BAL Cytokines Levels

Mean	IFN-γ	IL-10	IL-13	IL-1β	IL-4	IL-5	IL-6	KC/GRO	TNF-α
OVA/Saline	0.76 ± 0.33	3.13 ± 2.13	4.09 ± 7.13	11.3 ± 5.67	0.31 ± 0.11	15.6 ± 24.1	28.0 ± 35.8	214 ± 152	3.69 ± 9.97
OVA/OVA	1.04 ± 0.60	4.73 ± 4.39	17.9 ± 12.1	23.0 ± 13.9	0.56 ± 0.45	47.6 ± 44.9	145 ± 108	262 ± 88.6	65.9 ± 58.8
OVA/Dex 3mg/kg	0.62 ± 0.30	1.85 ± 1.42	3.49 ± 10.4	8.72 ± 3.48	0.23 ± 0.19	10.9 ± 14.5	23.0 ± 47.2	82.5 ± 45.0	3.85 ± 11.9

4 CONCLUSION

Based on this data, it is considered treatment with budesonide, betamethasone and dexamethasone are efficacious in the Brown Norway Rat OVA-induced pulmonary inflammation model and maybe used as clinically relevant reference agents.

5 ACKNOWLEDGMENT

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