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Title of Study
A Proof of Concept Study to Evaluate the Dose Response for the Systemic Benefit Risk Ratio of Inhaled Fluticasone Propionate in Chronic Obstructive Pulmonary Disease

Investigators
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Study centre(s)
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Publication (reference)
WILLIAMSON P, MENZIES D, CLEARIE K, VAIDYANTHATAN S, LIPWORTH B. Dose response for inhaled fluticasone on airway and systemic inflammation in COPD. Eur Respir J 2011;37:206-209

Objectives
To explore the risk/benefit of ICS in COPD by performing a pilot study of the corticosteroid dose-response relationship on airway and systemic inflammatory outcomes

Methodology
Double-blind, crossover study. Participants were randomised and grouped into treatment blocks of a 4-week dose ramp using 250 µg FP or placebo. Dose ramps consisted of 500 µg/day FP, followed by 2,000 µg/day for 2 weeks each, or a corresponding placebo. There was a steroid-free run-in and a wash-out between treatments, each of 2 weeks. Measurements were performed at baseline, after run-in and washout, and at 2 and 4 weeks of each treatment.

Number of patients planned
20 participants enrolled to complete 12

Number of patients analysed
18

Diagnosis and main criteria for inclusion
COPD. Current or ex-smokers, >50 years of age, with a FEV_1/FVC ratio <0.7, FEV_1 <80%, and reversibility <15% and 200 mL. The exclusion criteria were asthma and bronchiectasis.

Test product dose

Arm A
FP 250 µg (500 µg /day) (2 weeks)
FP 250 µg (2,000 µg/day) (2 weeks)

Arm B
Placebo (4 weeks)

Duration of treatment
8 weeks (2 treatment periods of 4 weeks)

Reference therapy
None

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Primary Endpoint
Serum C Reactive Protein and highly sensitive C- Reactive Protein

Secondary Endpoints
Overnight urinary cortisol to creatinine ratio, Spirometry and impulse oscillometry, Exhaled and alveolar nitric oxide, Serum cortisol, Serum osteocalcin, Serum IL-6 and TNF-α, Quality of Life Scores.

Statistical methods
Data were assessed for normality and non-Gaussian data were transformed prior to analysis. Values after run-in and washout periods were compared with a paired t-test to exclude carryover effects. Treatments were compared using ANOVA of repeated measures with planned contrasts between active treatments and for each active treatment compared to respective placebo. A priori calculations predicted an 80% power with 12 completed patients to detect a 50% reduction in CRP, with a two-tailed p-value <0.05, based on a study showing CRP suppression by ICS in COPD.

Results
We observed suppression of FeNO, JAW_{NO} and CA_{NO} with both doses of FP, and there was no significant dose response. Since cortisol was suppressed even at 500 µg/day FP, we cannot exclude a systemic effect to explain CA_{NO} suppression, rather than fine particle dose deposition into the small airways. The only outcome to show both suppression with 500 µg/day FP, and a dose response between moderate and high doses was morning cortisol. Similarly, OUCC showed a dose response and trend to suppression on 500 µg/day FP (p=0.08). Although this is the most direct marker of steroid activity, it re-enforces the potential harm of long-term ICS exposure relative to inflammation.

Conclusion
Despite long term benefits with ICS on exacerbations, COPD remains a relatively steroid-unresponsive condition, with a far greater dose–response relationship to adrenal suppression than systemic or airway inflammation.

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