728 Case Report: Addison's Disease From Inhaled Fluticasone 880 mcg/Day

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The patient is a 39-year-old female who had been initially on Pulmicort Turbuhaler 400 mcg twice a day for one year. Pulmicort was switched to Flovent MDI, 88 mcg twice a day for 3 months and then Flovent 220 mcg twice a day for one month. Due to continued cough, Flovent MDI 440 mcg twice a day with a spacer was started and 5 days of prednisone was added. The prednisone was 40 mg/day for 3 days, 20 mg day 4, 10 mg day 5. No other systemic steroids were given. Three months later she came in complaining of weakness and fatigue of one month's duration. She occasionally used Nasonex. Her physical exam revealed a sitting BP 142/90. She was somewhat tan and thin and had some bruising of her skin. The rest of the exam was unremarkable. As part of her evaluation, she had an undetectable 24 hour urine cortisol, an 8 a.m. serum cortisol less than 1 mcg/dl and a post ACTH 250 mcg cortisol of 4 mcg/dl with a normal stimulated ACTH cortisol greater than 20 mcg/dl. She had an ACTH of 10 pg/ml with a normal less than 70 pg/ml. CBC was normal, basic metabolic profile including electrolytes were normal. She had a normal MRI. These test results suggest 2° adrenal insufficiency due to central suppression of ACTH production by Flovent and possibly Nasonex, with normal mineralocorticoid activity suggested by normal BP and normal serum K+. The patient was placed on hydrocortisone with resolution of the weakness and fatigue. The Flovent dose was decreased and finally discontinued. The hydrocortisone was tapered gradually and discontinued. She moved to a different climate and her asthma symptoms resolved. The symptoms of fatigue and lack of energy have not returned. Her adrenal function has returned to normal. Fluticasone is the most lipophilic of the inhaled steroids (200-300 times greater than beclomethasone or budesonide and has the longest half-life (8-14 hours) after inhalation vs. 2-3 hours after inhalation for budesonide. The lipophilicity would make it the most likely steroid to cross the blood brain barrier and result in suppression of cortisol releasing factor in the hypothalamus. The low normal ACTH and the lack of response to ACTH stimulation would support this observation. The long half-life of fluticasone after inhalation (8-14 hours) when compared to other inhaled steroids would have additive side effects. Fluticasone is considered to be twice as potent as other inhaled steroids. Considering that we have the same corticosteroid receptor in all cells, this potency of fluticasone can result in more adverse side effects as this case report illustrates, particularly when you add the fact that fluticasone has the largest volume of distribution and longest half-life of all available inhaled steroids. We should not dismiss patients' complaints of weakness or fatigue if they are on inhaled steroids or nasal steroids until we evaluate their adrenal function.

729 Reduction of Eosinophil Counts by Montelukast in Double-Blind, Randomized, Placebo-Controlled Studies of Seasonal Allergic Rhinitis

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BACKGROUND: Montelukast is a cysteinyl leukotriene receptor antagonist that has shown benefit in improving symptoms of asthma while improving parameters of inflammation. Recent studies have examined montelukast for treatment of seasonal allergic rhinitis; effects on peripheral blood eosinophil counts were also analyzed in these studies.

METHOD: This series of 5 multicenter, double-blind, randomized, parallel group, placebo-controlled trials included 1029 males and 1762 females (ages 14 to 82 years) with active seasonal allergic rhinitis who were randomized to receive: montelukast 10 mg (n=813), loratadine 10 mg (n=1275), or placebo (n=703), each administered once daily for 2 weeks during the allergy season. Peripheral blood eosinophil counts were measured pre- and posttreatment.

RESULTS: The mean eosinophil count at baseline was 0.19 x 10^3 cells/μL for the montelukast group, and 0.20 x 10^3 cells/μL for both the loratadine and placebo groups. The mean absolute change from baseline to the end of the 2-week treatment period (LS mean ± SE) was -0.03 ± 0.00 for montelukast, -0.01 ± 0.00 for loratadine, and 0.00 ± 0.00 for placebo; the median percent change from baseline was -16.7% for montelukast, -2.2% for loratadine, and 0.0% for placebo. For comparisons between treatment groups, the differences in mean changes from baseline (LS mean with 95% Confidence interval) were -0.03 (-0.04, -0.02) for montelukast vs placebo and -0.01 (-0.02, 0.00) for loratadine vs placebo. Montelukast showed a significant reduction in peripheral blood eosinophil counts compared with placebo ($p<0.001$), whereas loratadine did not (p= NS).

CONCLUSION: These data demonstrate that patients with seasonal allergic rhinitis treated with montelukast 10 mg showed a significant reduction in peripheral blood eosinophilia, an important measure of systemic allergic inflammation.

730 Montelukast or Formoterol as Second-Line Therapy in Asthmatic Children Exposed to Allergens

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In allergic asthmatic children residents at high altitude, allergen-free environment, the re-exposure to allergens causes a deterioration of symptoms, lung function and bronchial hyperreactivity, associated with increase of inflammatory indices. In a single-blind randomized add-on study we compared the preventive effects of montelukast or formoterol added to low-dose budesonide. Lung function and airway inflammatory indices (exhaled nitric oxide and sputum eosinophils) were evaluated at T0, when the children were residents at high altitude and non-exposed to mites, and at T1, after 15 days of natural allergen exposure at sea level. After re-exposure, pulmonary function tests and sputum eosinophils remained stable in both the groups, without significant differences between T0 and T1. Furthermore, formoterol plus budesonide were effective in preventing the expected increase in eNO (SD+/-SEM) from T0 (26.4+/-2.6ppb) to T1 (29.3+/-9.2ppb)(ns). However, in the group receiving montelukast plus budesonide there was a significant decrease of eNO levels from baseline (30.7+/-6.8ppb) to T1 (18.1+/6.6)($p<0.05$). In asthmatic children the use of montelukast or formoterol combined with budesonide could offer a durable protective effect on symptoms and lung function. Furthermore, the addition of montelukast offers a further effect on bronchial inflammation.

731 Relative Transactivation and Transrepression Potencies of Fluticasone Propionate (FP) and Mometasone Furoate (MF)

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Glucocorticoids (GC) are the most effective anti-inflammatory drugs used in the treatment of asthma and allergy. By a process called transactivation, they increase the transcription of genes involved in either beneficial processes or certain side effects. Through transrepression, they inhibit the transcription factors Nuclear Factor-κ B (NF-κB) and Activator Protein-1 (AP-1), thereby decreasing the expression of many genes encoding inflammatory mediators such as the cytokine RANTES. The aim of the present study was to compare the transcriptional potencies of the topical corticosteroids FP and MF, using reporter gene assays. To test transrepression, we also measured FP and MF relative capacity to inhibit the production of RANTES using an immunoassay. In a previous study we had shown that these assays could help to predict the capacity of GC to produce side effects and anti-inflammatory effects. In transactivation assays, FP is slightly more

potent than MF ($EC_{50} \cong 10^{-10}$M versus 4×10^{-10}M), particularly at the highest concentrations, with a maximum of 40-fold inductions of reporter activity for FP as compared to 27-fold inductions for MF. However, there is no difference in the transactivating effects of FP and MF at concentrations reached in the plasma (peak $\cong 10^{-10}$M). Thus, there should be no difference in their ability to trigger systemic side effects. There are little differences in transrepression assays, FP being slightly more potent than MF at inhibiting NF-κB ($IC_{50} \cong 10^{-13}$M versus 2.5×10^{-13}M) and MF being slightly more potent than FP at inhibiting AP-1 ($IC_{50} \cong 4 \times 10^{-11}$M versus 5×10^{-11}M) in reporter gene assays. Nevertheless, in immunoassays, both drugs inhibited TNF-α induced RANTES release by 78% at 10^{-6}M, with an $IC_{50} \cong 10^{-10}$M. Thus, it seems that the differences between the transcriptional potencies of FP and MF, detected by reporter gene assays, are too small to be biologically and clinically relevant.

732 Effects of Leukotriene Receptor Antagonists on Bronchial Hyperresponsiveness: A Meta-Analysis

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BACKGROUND: Leukotriene receptor antagonists (LTRA's) are considered to have anti-inflammatory and bronchodilatory properties. Since bronchial hyperresponsiveness is intrinsic to the asthmatic disease process and is a surrogate marker of airway inflammation, we evaluated the bronchoprotection afforded at chronic dosing with LTRA's, namely montelukast (M)(n = 5 trials), pranlukast (P)(n = 4) and zafirlukast (Z)(n = 4).

METHODS: After initially identifying 70 trials, according to QUOROM criteria, a meta-analysis of 13 eligible randomised placebo controlled trials (total 353 patients) were included in which LTRA was given for 5 or more days. The primary end point was the doubling dose/dilution difference in PD_{20}/PC_{20} (with adenosine monophosphate, histamine and methacholine) between LTRA and placebo. Studies in which LTRA were given as 1st or 2nd line therapy were included.

RESULTS: Six trials used LTRA as first line therapy and 7 trials used LTRA as second line therapy. Only 1 trial had a 95% CI which included zero. A test of heterogeneity of the 13 trials was performed giving a Chi-squared value of 16.55; p = 0.22. Combining the results, the overall weighted estimate of protection amounted to a 0.9 (95% CI 0.7 to 1.0) doubling dose shift.

CONCLUSION: LTRA's confer a consistent degree of bronchoprotection when used as 1st or 2nd line therapy. This amounted to an overall protection of nearly 1 doubling dose (a clinically relevant difference), suggesting that LTRA's are of value as anti-inflammatory therapy in asthma.

733 Fluticasone Propionate/Salmeterol Diskus Combination Product Improves Asthma-Related Quality of Life Compared With Individual Components in Asthma Patients Symptomatic on β_2 Agonists Alone

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RATIONALE: Even in subjects with mild to moderate persistent asthma, symptoms can disrupt usual activities, depress emotional function and result in impairments in quality of life. The purpose of this study was to compare the effects of the fluticasone propionate/salmeterol combination product (FSC) 100/50mcg BID via DISKUS versus its individual components fluticasone propionate (FP) 100mcg BID and salmeterol (SAL) 50mcg BID on asthma-related quality of life in symptomatic patients suboptimally controlled on as-needed short-acting $\beta_2$agonists alone.

METHODS: Asthma-related quality of life was evaluated using the Asthma Quality of Life Questionnaire (AQLQ) in a 12-week, randomized, double-blind, active-controlled, parallel-group study comparing the safety and efficacy of FSC with FP and SAL alone in symptomatic patients aged ≥12 years with FEV_1 40-85% predicted and ≥15% reversibility (SAS30017). A total of 259 out of 267 patients completed an AQLQ at baseline and endpoint. Mean baseline overall AQLQ score was 4.34 on a 7-point scale, with 1 indicating maximum impairment and 7 indicating no impairment in asthma-related quality of life.

RESULTS: Mean change in overall AQLQ score from baseline at endpoint was clinically meaningful (≥0.5) in all three treatment groups: FSC (1.50), FP (0.95) and SAL (1.13). Improvement in overall AQLQ score in the FSC group was significantly greater compared with FP (raw difference=0.55, p=0.028) and SAL (raw difference=0.37, p=0.009). Further, 85% of subjects treated with FSC demonstrated a clinically meaningful increase in overall AQLQ score from baseline at endpoint compared with only 67% in the FP group and 71% in the SAL group (p=0.056).

CONCLUSIONS: Using the combination product FSC as initial maintenance therapy to treat the two main components of asthma—inflammation and bronchoconstriction—in symptomatic patients previously using short-acting β_2 agonists resulted in clinically meaningful improvements in asthma-related quality of life that were significantly greater compared with either of the individual components alone. Funded by: GlaxoWellcome.

734 Efficacy of Budesonide Inhalation Suspension (Pulmicort Respules™) in Children With Asthma Previously Treated With Inhaled Corticosteroids or Other Daily Medications

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Three US randomized, 12-week, double-blind, placebo-controlled, parallel-group trials (Kemp et al, *Ann Allergy Asthma Immunol* 1999;83:231; Shapiro et al, *J Allergy Clin Immunol* 1998;102:789; Baker et al, *Pediatrics* 1999;103:414) showed that nebulized budesonide inhalation suspension (BIS) was efficacious and well tolerated in children with asthma. The objective of this retrospective, integrated analysis of these 3 trials was to assess the efficacy of BIS in children who were/were not treated with another inhaled corticosteroid (ICS) before study entry. The children, aged 6 mo - 8 yr, had symptomatic persistent asthma treated with at least 1 daily maintenance medication before enrollment. Patients were randomized to placebo or BIS administered via nebulizer and compressor qd or bid at dosages of 0.25-2.0 mg/d. Patients or their parents/guardians recorded daytime and nighttime asthma symptoms daily on a 0 (no symptoms) to 3 (severe symptoms) ordinal scale. Results are shown below. BIS reduced symptoms in patients still symptomatic despite previous treatment with another ICS or nonsteroidal maintenance medications. Patients previously treated with another ICS but still symptomatic at study entry had the larger effect of BIS relative to placebo. The lack of a placebo effect in this subgroup attests to the need for an effective antiinflammatory agent for these children.

Changes in Daytime and Nighttime Symptom Scores

Baseline Medication	Treatment Group	N	Baseline Mean	LS Mean Change from Baseline (from ANCOVA)	Placebo vs BIS Difference (from ANCOVA) LS Mean (95% CI)	P
Daytime Symptoms						
ICS	BIS	307	1.30	-0.44	0.34 (0.22, 0.46)	< .001
	Placebo	97	1.30	-0.10		
Other	BIS	471	1.33	-0.47	0.13 (0.02, 0.24)	.019
	Placebo	131	1.27	-0.34		
Nighttime Symptoms						
ICS	BIS	306	1.12	-0.33	0.33 (0.21, 0.45)	< .001
	Placebo	97	1.19	0.00		
Other	BIS	472	1.26	-0.42	0.15 (0.05, 0.26)	.005
	Placebo	131	1.09	-0.27		

MONDAY