616 Suppression of IL-13-Associated Gene Signature in Airway Epithelial Cells By Dexamethasone Is Decreased in Poorly Controlled Asthma

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RATIONALE: Asthma is associated with the metaplastic transformation of airway epithelial cells (EpC), a process stimulated in part by the cytokine IL-13 that drives mucus hypersecretion and bronchial hyperreactivity. This IL-13-inducible transformation is associated with the expression of a stereotypic gene signature including SerB2, CLCA1, and periostin and the IL-13-induced expression of these genes is normally suppressed by corticosteroids (CCS). Poor symptom control in children with asthma may be associated with insensitivity to the anti-inflammatory effects of corticosteroids. We investigated the ability of physiological concentrations of dexamethasone (dex) to inhibition expression of SerB2, CLCA1, and periostin in EpCs obtained from children with controlled (n=3) and poorly-controlled (n=10) asthma.

METHODS: Children with asthma underwent bronchoscopy to evaluate refractory wheeze or suspected structural anomalies and grouped according to the level of asthma control by the cACT (childhood asthma control test). Fresh EpC were obtained via endobronchial brushings and cultured in the absence or presence of a physiological concentration of dexamethasone (10^{-9}M) and alterations in gene expression expressed via quantitative PCR.

RESULTS: Baseline expression of CLCA1 but not periostin or SerB2 was higher ($p = 0.04$) in children with poorly- versus well controlled asthma. Dexamethasone inhibited the expression of the three IL-13 inducible gene signature products in controlled but not poorly-controlled children with asthma.

CONCLUSIONS: In children with controlled asthma, bronchial EpCs demonstrated CCS-mediated inhibition of the IL-13-inducible gene signature SerB2, CLCA1, and periostin. In contrast, EpC from poorly-controlled asthmatics failed to show this response. Severe, poorly-controlled asthma reflects in part corticosteroid non-responsiveness of bronchial epithelial cells.

617 Predictive Factors of Reaction Severity during Standardized Aspirin Desensitization in Aspirin-Exacerbated Respiratory Disease (AERD).

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RATIONALE: Aspirin desensitization is effective therapy for AERD and has been successfully and safely performed for hundreds of patients at Scripps Clinic. However, data to predict severe reactions is lacking.

METHODS: A chart review of 275 patients with AERD who underwent aspirin desensitization at Scripps Clinic from January 2009 through August 2015 was performed. Of those, 204 met inclusion criteria. Pre-challenge characteristics, such as baseline FEV_1, baseline ACT, and medication use were analyzed. Each challenge was reviewed to quantify the reactors, type and severity of reaction, medications used for treatment, and length of desensitization. The data was analyzed to identify characteristics that might predict a severe reaction.

RESULTS: One hundred sixty-seven (81.8%) patients reacted during challenge, and desensitization was successful in all of them. One hundred forty-seven (88.0%) reacted to nasal ketorolac and 63 (37.7%) to oral aspirin. Naso-ocular reactions were more common among ketorolac reactors. Twenty-one patients were considered severe reactors based on IM epinephrine use or FEV_1 drop $\geq$ 30% and/or $\geq$ 3 bronchodilator treatments. All severe reactors were successfully desensitized as outpatients. Average length of desensitization was 1.67 days (range: 1 to 4 days). GI reactors required an average of 2.29 days (p=0.006).

CONCLUSIONS: Despite undergoing the same aspirin desensitization protocol, approximately 10% of subjects had severe reactions. The likelihood of GI reactions during desensitization is greater if a GI reaction occurred with prior COX-1 inhibitor exposure, but not all patients with a GI reaction during desensitization report such history. A higher baseline SNOT-22 score was associated with more severe reactions (p=0.05).

618 Expression of Corticosteroid Regulated Genes By Peripheral Blood Mononuclear Cells (PBMCs) in Children from the NIH/Niaid Sponsored Asthma Phenotypes in the Inner City (APIC) Study after One Year of Guidelines-Based Therapy

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RATIONALE: The development of peripheral blood markers for characterization of therapeutic responses to corticosteroids in asthma is of great importance.

METHODS: PBMC were collected from 125 asthmatic children (ages 6-17) after one-month (Visit 0, V0) and one year (Visit 6, V6) of NAEPP guidelines-based therapy. At V6, patients were categorized as difficult-to-control, easy-to-control and indeterminate per APIC study definition. PBMC expression of glucocorticoid receptor alpha (GRalpha), corticosteroid transactivation (FK binding protein 5 (FKBP5)) and transrepression markers (IL-8, TNFalpha) at baseline and in response to 10^{-8}M fluticasone were determined by RT-PCR. Matched V0 and V6 PBMC data from 95 patients were analyzed.

RESULTS: 31, 19 and 45 patients were categorized as easy-to-control, indeterminate and difficult-to-control, respectively. PBMC of difficult-to-control as compared to easy-to-control patients had significantly decreased GRalpha at V0 (p=0.05). Compared to easy-to-control patients, corticosteroid-mediated transrepression remained poor in PBMC of difficult-to-control patients at V6, with significantly decreased TNFalpha and IL-8 fold suppression by fluticasone at V6 compared to easy-to-control patients, even after adjusting for TNFalpha or IL-8 fold suppression by fluticasone at V0 (p=0.001 and p=0.02, respectively). Contrary to easy- and difficult-to-control patients, baseline TNFalpha did not decline between V0 and V6 in indeterminate patients (p=0.035 and p=0.008 respectively). Compared to indeterminate subjects, corticosteroid-mediated transactivation improved in the PBMC of difficult-to-control patients at V6, with increased FKBP5 induction by fluticasone at V6 (p=0.03).

CONCLUSIONS: This is the first study to demonstrate reduced responsiveness to corticosteroids in PBMC of difficult-to-control asthma patients over the course of one year of the asthma guidelines-based therapy.