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^-8M 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.