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Mepolizumab Alters Regulation of Airway Type-2 Inflammation in Urban Children with Asthma by Disrupting Eosinophil Gene Expression but Enhancing Mast Cell and Epithelial Pathways

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387 Onset of Clinical Effect with Sublingual Immunotherapy Tablets for Allergic Rhinoconjunctivitis

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RATIONALE: Knowledge is limited regarding the minimum duration of time needed to induce allergen-specific tolerance and clinical improvement with immunotherapy for allergic rhinitis/conjunctivitis. Onset of clinical effect was evaluated for grass, ragweed, tree, and house dust mite (HDM) sublingual immunotherapy (SLIT)-tablets.

METHODS: Efficacy from phase 3 field trials of 2800 BAU grass (NCT00227279, N=634), 12 Amb a 1-U ragweed (NCT00783198, N=565), and 12 SQ-Bet tree (EudraCT-2015-004821-15, N=634) SLIT-tablets was assessed by allergic rhinitis/conjunctivitis daily symptom score (DSS) or total combined score (TCS, sum of DSS and medication scores). Treatment began ≥12-16 weeks before the pollen season and continued throughout the season. Efficacy of the 12 SQ-HDM HDM SLIT-tablet was assessed by total nasal symptom score (TNSS) during challenge in an environmental exposure chamber trial (NCT01644617, N=124) at 8 weeks and later.

RESULTS: A 30% DSS reduction versus placebo (P<0.0001) with the grass SLIT-tablet was observed over the entire pollen season, with a 38% reduction the first week of the season. A 40% and 26% TCS reduction versus placebo (P<0.001) with the tree and ragweed SLIT-tablets, respectively, was observed over the entire pollen season; TCS scores clearly separated from placebo within the first 2 weeks of the season. A 20% TNSS reduction versus placebo (P=0.007) with the HDM SLIT-tablet was observed at 8 weeks, the earliest chamber challenge.

CONCLUSIONS: Patients starting grass, ragweed, or tree SLIT-tablets ≥12-16 weeks before the respective pollen season can expect onset of clinical effects during the first respective pollen season and as early as 8 weeks with the HDM SLIT-tablet.

388 Comprehensive analysis of epigenome and transcriptome-based correlation network analysis in severe asthma risk prediction

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RATIONALE: Asthma is a chronic inflammatory disease of the airways associated with epigenetic and genetic risk factors. Co-expressed and co-methylated gene modules-based approaches can identify gene sets that are specifically asthma-associated biological process beyond known candidate genes. However, limited studies reported predictive models associated with asthma severity and lung function based on genome-wide weighted correlation network analysis (WGCNA) and machine learning (ML) methods.

METHODS: We performed epigenome and transcriptome analyses (n =142) using WGCNA to identify significantly co-methylated and co-expressed modules associated with asthma severity and lung function. We used ML approaches to select differentially methylated and expressed genes followed by methylation risk score (MRS) and transcriptomic risk score (TRS) based risk predication.

RESULTS: There were 18 methylated and 28 differentially expressed genes significantly associated with asthma status. The risk prediction model revealed MRS (AUC = 0.91), TRS (AUC = 0.97) and the jointed analysis (MRS +TRS) with AUC = 0.98. MRS and TRS were strongly associated with asthma severity and FEV1 (P < 0.001). An independent validation showed that TRS (AUC=0.86) was a better predictor of asthma risk than MRS (AUC= 0.66). Moreover, integrated analysis of asthma-severity associated co-methylation and co-expression modules showed enriched biological pathways including Th1 and Th2 cell differentiation and notch signaling.

CONCLUSIONS: Overall, the finding suggests the utility of multi-omics-based risk score models for asthma risk prediction, and our approach could serve as reliable method for asthma diagnosis.

389 Mepolizumab Alters Regulation of Airway Type-2 Inflammation in Urban Children with Asthma by Disrupting Eosinophil Gene Expression but Enhancing Mast Cell and Epithelial Pathways

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RATIONALE: Mepolizumab (anti-IL5) reduces asthma exacerbations in urban children. We previously utilized nasal transcriptomics to identify inflammatory pathways (gene co-expression modules) associated with exacerbations despite this therapy. To understand mepolizumab's precise impact on these pathways, we assess gene co-expression and loss of correlation, "decoherence," using differential co-expression network analyses.

METHODS: 290 urban children (6-17 years) with exacerbation-prone asthma and blood eosinophils ≥150/microliter were randomized (1:1) to q4 week placebo or mepolizumab injections added to guideline-based care for 52 weeks. Nasal lavage samples were collected before and during treatment for RNA-sequencing. Differential co-expression of gene networks was evaluated to assess interactions and regulatory aspects of type-2 and eosinophilic airway inflammation.

RESULTS: Mepolizumab, but not placebo, significantly reduced the overall expression of an established type-2 inflammation gene co-expression module (fold change=0.77, p=0.002) enriched for eosinophil, mast cell, and epithelial IL-13 response genes (242 genes). Mepolizumab uncoupled co-expression of genes in this pathway. During mepolizumab, but not placebo treatment, there was significant loss of correlation among eosinophil-specific genes including *RNASE2* (EDN), *RNASE3* (ECP), *CLC*, *SIGLEC8*, and *IL5RA* contrasting a reciprocal increase in correlation among mast cell-specific genes (*TPSAB1*, *CPA3*, *FCER1A)*, T2 cytokines (*IL4*, *IL5*, and *IL13*), and *POSTN*.

CONCLUSIONS: These results suggest mepolizumab disrupts the regulatory interactions of gene co-expression among airway eosinophils, mast cells and epithelium by interrupting transcription regulation in eosinophils with enhancement in mast cell and epithelial inflammation. This paradoxical effect may contribute to an incomplete reduction of asthma exacerbations and demonstrates how differential co-expression network analyses can identify targets for more precise therapies.

SATURDAY