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Distinct Airway Inflammatory Pathways Associated with Asthma Exacerbations are Modulated by Mepolizumab Therapy in Children

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SUNDAY

440 Phenotype-directed Therapy with Mepolizumab for Urban Children with Exacerbation-Prone Asthma

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RATIONALE: Asthma exacerbations are common in urban children and have significant short- and long-term consequences. Elevated peripheral blood and airway eosinophils have been identified as risk factors for exacerbations, and therapies targeting these biomarkers reduce exacerbations in adults; however, data on anti-eosinophil treatment in children and adolescents are limited. The primary objective of this study is to determine if phenotype-directed use of mepolizumab reduces the rate of asthma exacerbations in urban children.

METHODS: Urban children 6-17 years of age (n=290) with exacerbation-prone asthma (2+ exacerbations in previous year) and blood eosinophils ≥150/mm^3 were randomized 1:1 to mepolizumab (6-11 years: 40 mg; 12-17 years: 100 mg) or placebo every 4 weeks added to guideline-based care for 1 year. The primary outcome was the number of asthma exacerbations treated with systemic corticosteroids; a comparison of the two treatment groups was evaluated using a negative-binomial model.

RESULTS: Mepolizumab significantly reduced peripheral blood eosinophils ($p<0.01$) and nasal eosinophils ($p<0.01$). The rate of asthma exacerbations was significantly lower in mepolizumab (0.96 exacerbations/year) vs. placebo (1.30 exacerbations/year) treated participants [relative risk 0.73 (95% confidence interval 0.56-0.96), $p=0.027$]. There were no significant differences in secondary outcomes, including time to first exacerbation, lung function, quality of life, or composite asthma severity index (CASI). *Post hoc*, the time to second asthma exacerbation increased significantly with mepolizumab ($p=0.02$). Adverse events were similar between groups.

CONCLUSIONS: Phenotype-directed therapy with mepolizumab in urban children and adolescents with exacerbation-prone eosinophilic asthma significantly reduced recurrent exacerbations and was well tolerated, but did not impact other asthma outcomes.

441 Distinct Airway Inflammatory Pathways Associated with Asthma Exacerbations are Modulated by Mepolizumab Therapy in Children

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RATIONALE: Identification of specific airway inflammatory pathways can lead to effective personalized treatment with biologics in asthma and insights to mechanisms of action.

METHODS: 290 urban children with exacerbation-prone asthma and ≥150/mm^3 blood eosinophils were randomized (1:1) to placebo or mepolizumab added to guideline-based care. Nasal lavage samples were collected at randomization and during treatment for RNA-sequencing, and analyzed by cell-deconvolution modular analysis to assess genome-wide expression patterns associated with exacerbation number and effect of treatment.

RESULTS: Mepolizumab significantly reduced the frequency of exacerbations compared to placebo. At randomization, there were no differences in expression between treatment groups; multiple modules were subsequently differentially expressed during mepolizumab but not placebo treatment. Furthermore, expression levels of multiple modules were associated with the exacerbation number during the study, with distinct relationships observed in the placebo and/or mepolizumab groups. Notably, higher expression at randomization of an eosinophil-associated module enriched for Type-2 genes including *IL4*, *IL5*, and *IL13*, was associated with increased exacerbations in placebo ($\beta=0.19$, $p<0.001$), but not mepolizumab-treated children (interaction $p<0.01$). Furthermore, mepolizumab treatment reduced expression of this module (Fold-change=0.62, $p<0.001$). In contrast, higher expression at randomization of an eosinophil-associated module enriched for eosinophil activation (e.g. *CD9*) and mucus hypersecretion (e.g. *MUC5AC*) genes was associated with exacerbation number in both groups throughout the study ($\beta=0.18$, $p<0.01$) and was unaltered by mepolizumab therapy.

CONCLUSIONS: Multiple distinct airway inflammation patterns were identified associated with exacerbation frequency. These findings identify inflammatory endotypes and indicate likelihood and potential mechanisms of a beneficial clinical response to mepolizumab therapy to prevent exacerbations.