Cluster analysis of inflammatory biomarker expression in the International Severe Asthma Registry (ISAR)

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Introduction/Aim: Allergy, eosinophilic inflammation, and epithelial dysregulation are implicated in severe asthma pathogenesis. We characterized biomarker expression in adults with severe asthma.

Methods: Within the International Severe Asthma Registry (ISAR), we analyzed data from 10 countries in North America, Europe and Asia, with pre-specified thresholds for biomarker positivity (serum IgE ≥75kU/L, blood eosinophils ≥300 cells/uL, and FeNO ≥25ppb), and with hierarchical cluster analysis using biomarkers as continuous variables.

Results: Of 1175 patients; 64% were female, age (mean±SD) 53±15 years, body mass index (BMI) 30±8, post-bronchodilator FEV_1 predicted 74±20%. By pre-specified thresholds, 59% were IgE positive, 57% eosinophil positive, and 58% FeNO positive. There was substantial overlap; 59% were positive for either two or three biomarkers. Five distinct clusters were identified: **Cluster 1** (61%, low-to-medium biomarkers) comprised highly symptomatic, older females with elevated BMI and frequent exacerbations; **Cluster 2** (18%, elevated eosinophils and FeNO) older females with lower BMI and frequent exacerbations; **Cluster 3** (14%, extremely high FeNO) older, highly symptomatic, lower BMI and preserved lung function; **Cluster 4** (6%, extremely high IgE) younger, long duration of asthma, elevated BMI, and poor lung function; **Cluster 5** (1.2%, extremely high eosinophils) younger males with low BMI, poor lung function, and high burden of sino-nasal disease and polyposis.

Conclusion: There is significant overlap of biomarker positivity in severe asthma. Distinct clusters according to biomarker expression exhibit unique clinical characteristics, suggesting the occurrence of discrete patterns of underlying inflammatory pathway activation and providing pathogenic insights relevant to the era of monoclonal biologics.

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