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Molecular Analysis of IL-5 Receptor Subunit Alpha as a Possible Pharmacogenetic Biomarker in Asthma

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Background: Asthma is a heterogeneous syndrome with a broad clinical spectrum and high drug response variability. The inflammatory response in asthma involves multiple effector cells and mediator molecules. Based on asthma immunopathogenesis, precision medicine can be a promising strategy for identifying biomarkers. Biologic therapies acting on the IL-5/IL-5 receptor axis have been developed. IL-5 promotes proliferation, differentiation and activation of eosinophils by binding to the IL-5 receptor, located on the surface of eosinophils and basophils. This study aimed to investigate the expression of *IL5RA* in patients with several types of asthma and its expression after treatment with benralizumab, a biologic directed against IL-5 receptor subunit alpha.

Methods: Sixty peripheral blood samples, 30 from healthy controls and 30 from asthmatic patients, were selected for a transcriptomic RNAseq study. Differential expression analysis was performed by statistical assessment of fold changes and *P*-values. A validation study of *IL5RA* expression was developed using qPCR in 100 controls and 187 asthmatic patients. The effect of benralizumab on *IL5RA* expression was evaluated in five patients by comparing expression levels between pretreatment and after 3 months of treatment. The *IL5RA* mRNA levels were normalized to *GAPDH* and *TBP* expression values for each sample. Calculations were made by the comparative $\Delta\Delta$Ct method. All procedures followed the MIQE guidelines.

Results: *IL5RA* was one of the most differentially overexpressed coding transcripts in the peripheral blood of asthmatic patients ($P = 8.63E\text{-}08$ and fold change of 2.22). In the qPCR validation study, *IL5RA* expression levels were significantly higher in asthmatic patients than in controls ($P < 0.001$). Significant expression differences were present in different asthmatic types. In the biological drug study, patients treated with benralizumab showed a significant decrease in *IL5RA* expression and blood eosinophil counts. A notable improvement in ACT and lung function was also observed in these patients.

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