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PHARMACOGENOMICS OF ASTHMA TREATMENT

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Introduction

Asthma is most common chronic disease of childhood. Asthma is inflammatory disease of unknown etiology. We usually treat asthma with corticosteroids or anti-leukotriene drugs. As symptom relieving drugs asthmatics use bronchodilators – usually beta2 receptor agonists. There are substantial differences in the effect of antiasthmatic therapy between individuals which are related to different genetic code. Single nucleotide polymorphisms (SNPs) in α2 adrenergic receptor gene (α2AR)[1] and corticotropine releasing hormone receptor 1 (CRHR1)[2] have been recently associated with treatment outcome in asthma. In our study we corellated polymorphisms in α2AR, ALOX5, CRHR1 and MDR1/ABCB1 genes with clinical features and treatment outcome in Slovenian childhood asthma patients.

Methods

We enrolled 100 Slovenian patients with childhood asthma and their parents for disease association and pharmacogenomic studies. Patients were children aged from 6 to 18 years with mild persistent asthma, which were diagnosed according to American Thoracic Society criteria.[3] They also had no other chronic disease. We obtained informed consent from above 15 years old patients and from parents for younger patients. We first examined allergic status with skin prick test. In all children we measured spirometry, PD20 with metacholine bronchoprovocation test and nitric oxide in exhaled air. We also measured FEV1 before and after inhalation of bronchodilator – albuterol (3 puffs with MDI). Asthmatic children measured PEF at home for at least two weeks and wrote values in diary. From same venepuncture we also used blood for analysis of total IgE, specific IgE and number of eosinophils in peripheral blood. In addition to 100 patients with previous antiasthmatic treatment we enrolled 20 children without previous antiasthmatic treatment in the prospective study. According to NAEEP guidelines we started to treat all children with fluticasone propionate.[4] They took medication for at least 4–6 months. First outpatient visit was after 4–6 weeks, then after 12–14 weeks and finally at the end of the study 4–6 months after start of therapy. DNA, RNA and proteins were isolated from peripheral blood leucocytes using Tri reagent (Sigma). We used RFLP and Taqman methods for SNP genotyping. We used t-test and χ^2 statistics and SPSS program for statistical analysis.

Results

Before therapy overall variation of PEF was 39.2 % (95 % CI, 34.2–44.2), PD20 was 0.21 mg of metacholine (95 % CI, 0.16–0.26), eNO 46.2 ppb (95 CI, 38.0–54.4), blood total IgE 885 IU/ml (95 % CI, 443–1327) and number of eosinophils in mm^3 of blood 701 (95 % CI, 617–785). We found Arg16Gly SNP in α2AR associated with treatment outcome, patients with genotype Arg/Arg had worse outcome and decrease in PEF values of 20.8±10.5 L/min after regular beta2 receptor agonists treatment. In patients with Arg/Arg genotype FEV1 increased for only 6.9 ± 5.5 % after application of albuterol which is significantly less than 13.2±8.4 % in patients with Gly/Gly genotype (p = 0.01). We also found SNP rs242941 in CRHR1 gene is associated with response to corticosteroid treatment. In patients with wild type genotype G/G, FEV1 increased for 16.4±9.1 % what is significantly better than increase of FEV1 for 7.7±7.9 in patients with genotype T/T (p = 0.02).

Conclusions

We have confirmed genetic variation in α2AR and CRHR1 genes associatied with treatment outcome in Slovenian childhood asthma patients. Identification of additional genes

associatied with treatment outcome will enable to contruct genetic profiles which should improve the clinical relevance of using pharmacogenetic data for prediction of treatment outcome in asthma patients.

References

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