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Pharmacogenomic of asthma in children

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ABSTRACT

Asthma is an inflammatory airway disease characterized by bronchial hyper-responsiveness, reversible airflow limitation, and respiratory symptoms. Asthma affects 300 million people in developed countries. More than 10% of asthma complaints in children occur at school age. Asthma therapy in children using pharmacological agents is still the main choice until now. However, the response of pediatric patients to asthma treatment varies. In addition to age, organ function, and drug interactions, genetic factors are often associated with drug response variability. This variability can occur due to single nucleotide polymorphisms (SNP) in protein-coding genes that play a role in bioavailability and drug response. Understanding of pharmacogenomics as the basis of individualized medicine aims to avoid adverse drug reactions and maximize drug effectiveness. The existence of genetic variation allows the drug response between individuals to be different. Pharmacogenomics provides important information in individual-based medicine so that it can predict the existence of a population that can respond well to certain drugs and a population that has a higher risk of adverse drug reactions. Implementation of individual treatment can optimize treatment in patients because the dose of treatment and therapeutic options have been adjusted based on individual genetic characteristics.

ABSTRAK

Asma adalah penyakit inflamasi kronis saluran napas yang ditandai dengan hiper-responsif bronkus, hambatan aliran udara yang reversibel, dan gejala pernapasan. Asma mempengaruhi 300 juta penduduk pada negara maju. Lebih dari 10% keluhan asma pada anak anak terjadi pada usia sekolah. Terapi asma pada anak menggunakan agen farmakologi masih menjadi pilihan utama hingga saat ini. Namun respon pasien anak-anak terhadap pengobatan asma bervariasi. Selain faktor usia, fungsi organ, dan interaksi obat, saat ini faktor genetik sering kali dikaitkan dengan variabilitas respon obat. Varibilitas tersebut dapat terjadi akibat *single nucleotide polymorphisms* (SNP) pada gen penyandi protein yang berperan dalam bioavailabilitas dan respon obat. Pemahaman farmakogenomik sebagai dasar dari *individualized medicine* bertujuan untuk menghindari efek obat yang merugikan dan memaksimalkan efektivitas obat. Adanya variasi genetik memungkinkan respon obat antar individu berbeda. Farmakogenomik memberikan informasi penting dalam pengobatan berbasis individu sehingga dapat memprediksi adanya populasi yang dapat merespons obat tertentu dengan baik dan populasi yang memiliki risiko lebih tinggi terhadap reaksi obat yang merugikan. Implementasi *individualized medicine* dapat mengoptimalkan pengobatan pada pasien karena rejimen dosis dan pilihan terapi telah disesuaikan berdasarkan karakteristik genetik individu.

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INTRODUCTION

Asthma is a chronic inflammatory airway disease characterized by bronchial hyperresponsiveness, reversible airflow limitation, and respiratory symptoms. Asthma affects 300 million people in developed countries.[1] Clinical symptoms of asthma are recurrent wheezing, coughing, chest tightness, and dyspnea, then with night and early morning symptoms become more frequent and reduce quality of life. Complaints of asthma in children at school age about 10-15%.[2] The severity of symptoms decreases at the beginning of puberty and can even disappear in those with mild acidity.[3]

Asthma in older children is characterized by histopathology of chronic inflammatory processes in the conducting airways. Epithelial sloughing is seen with inflammation and edema of the airway walls. Genetic predisposition, in combination with allergens and viral infections, may contribute to the development of asthma.[4] The severity of asthma in children is more difficult than that in adult patients, because pediatric patients have a pattern of exacerbations that develops rapidly, frequently, and frequently recurs. Children experiencing severe exacerbations can be triggered by a viral infection or caused by an allergen. Periodic assessment of asthma phenotype in children can influence treatment.[5] About 60-75% of school-age children with asthma have been exposed to one or more allergens, asthma can also occur in the absence of allergic sensitization. The phenotype of persistent wheezing, coughing, and chest tightness is increasingly recognized in nonallergic individuals. As a result, asthma is viewed as a diverse disease phenotype with many subphenotypes.[3]

Pharmacogenetics is now increasingly being studied and used in children.[6] Pharmacogenomic treatment is a genetic test that helps assess and explain the patient's response to treatment, so that it can help make better drug and dose selection.[7] Pharmacogenemic testing involves the analysis of gene variants associated with drug metabolism and transport or treatment targets. Differences in drug response between individuals are an important consequence of toxicity in treatment, hence the proposed genetic predisposition for individual treatment variations in the treatment response of patients in children.[8] The benefits of pharmacogenetics are increasing the therapeutic response to treatment and reducing the response to adverse side effects.[9] This side effect, if not handled properly, will reduce the patient's adherence to using the drug in their treatment.[10]

The majority of pharmacogenomic studies have been conducted in adults, but it is important to remember that adult findings cannot be directly applied to pediatric patients. Children are still developing processes and systems such as metabolic systems, hemostasis, and drug biotransformation.[11] The use of drugs has different effects in children and in adults. Despite persistent genetic variation, the contribution to treatment heterogeneity at younger ages will be different. A major challenge in asthma is predicting the efficacy of bronchodilator drugs. This review article highlighted the use of pharmacogenomics in children, and the potential of pharmacogenomics to improve and adapt treatment for children.

MATERIALS AND METHODS

The type of review used in this article is in the form of a systematic review using the PubMed database, Google Scholar, with the keywords "benefits", "risks", "pharmacogenomics" and "treatment in children". With the criteria of articles being reviewed in a 10-year period until August 2021. Articles were collected in August 2021, with the keywords "pharmacogenemic" or "single nucleotide polymorphism" or "pediatric medicine" or "asthma" on PubMed and Google Scholar websites.

RESULT

Pharmacogenomics in pediatrics

The study of genetics influencing drug response is known as pharmacogenomics. Better patient therapy can result from a better understanding of the genetic factors of drug response. Pharmacogenomics aims at the individualized treatment of asthma by identifying patients who are at risk of severe toxicity or who would benefit from a particular treatment based on the patient's genetic profile. Furthermore, pharmacogenomics provides a new tool to identify new drug targets. β2-Agonists, leukotriene antagonists, and glucocorticosteroids have been the focus of asthma pharmacogenomics research so far.[12]

Pharmacogenomic studies have been carried out in adults, but the results in adults can not be directly applied to pediatric patients. Pediatric patients are still developing processes and systems such as metabolism, hemostasis, and drug biotransformation.[11] Pharmacogenomic treatment is a genetic test that helps assess and explain the patient's response to treatment, so that it can help make better drug and dose selection.[13]

Diseases such as asthma, autism, attention- deficit hyperactivity disorder (ADHD), juvenile rheumatoid arthritis and epilepsy occur during childhood. If they do not treated with proper treatment there will be adverse reaction drug (ADR) which is a significant death in pediatric patient.[14]

Asthma phenotypes differ between children and adults.[15] A genetic variant affecting FBXL7 expression was found by the CAMP group to be associated with improved asthma symptoms in response to inhaled corticosteroids in two pediatric populations, but it failed to replicate in adults.[16] Several Genome-Wide Association Studies (GWAS) of response to asthma treatment have been published by the CAMP study group[17] and can be found in the National Human Genome Research Institute and the European Bioinformatics Institute (NHGRI-EBI).[18]

Identifying toxicity in children takes a long time because side effects take a long time to manifest in pediatric patients. Specific strategies in children are urgently needed to investigate the genetic basis underlying inter-patient variability in drug response.[19] Pharmacogenomic treatment will be useful in providing genetic markers of increased risk or susceptibility, then providing information on the genetic status of pediatric patients before treatment. It will be easier to determine patients who are suitable for certain therapeutic treatments and avoid the occurrence of ADR and serious complications that are potentially life-threatening in pediatric patients.[20] The individual patient's response to medication is influenced by a number of factors, including disease etiology, adherence, disease severity, and genetic profile. The major goal of pharmacogenetics is to predict the response to treatment efficacy or the risk of ADR in the pediatric population, and that the genotype of individuals prior to treatment.[21]

Asthma treatment pharmacogenetics

Response β_2- agonist

Asthma is the most common chronic disease in children. Asthma is treated with a stepwise approach.[11] β_2-Agonists are the most commonly prescribed drugs for the treatment of asthma. One of the best-characteristic genes in asthma pharmacogenetics is β2-adrenergic receptor gene (*ADRβ2*) encoding β2-adrenergic receptors (ARβ2). Several SNPs have been identified and associated with treatment response. The SNPs located in the *ADRβ1* and *ADRβ2* have been associated with a bronchodilator response (BDR) in both adults and children with asthma. Other gene variants associated with airway inflammation via the nitric oxide pathway have also been associated with BDR.[22]

*β*2-Agonists work by binding to receptors ADRβ2, which are G-protein-coupled receptors on the cell surface. The ARβ2 contains several polymorphisms, including Arg16Gly and Gln27Glu, which are functionally relevant. Patients who are homozygous for Arg16 have lower clinical outcomes and show unfavorable consequences than those who are homozygous for Gly16.[23]

Short acting *β*2 agonists (SABA), for example: salbutamol, albuterol, and terbutaline are the initial therapy prescribed to relieve symptoms of bronchoconstriction.[24] Two genetic variants have been associated with SABA. Bronchodilator response on SABA use was also assessed as an outcome in GWAS. Genetic variation in SPATA13 and its associated antisense RNA found to be associated with the BDR.[25]

Long acting *β*2 agonists (LABA) for example: salmeterol and formoterol, act on ARβ2 which is the same as SABA, but works longer (8-12 h, compared to 3-5 h for SABA). LABAs are not prescribed as needed, but as primary maintenance treatment in combination with corticosteroids to avoid the increased risk of side effects associated with LABA monotherapy. The Arg16 variant may have an impact on LABA outcomes, but particularly in the pediatric asthmatic population. A rare variant in ADRβ2 has been associated with an increased risk of asthma-related hospitalization.[25]

Inhaled corticosteroids

Inhaled corticosteroids are very effective in treating asthma in children and adults. Inhaled corticosteroids are added to the regimen if asthma symptoms persist to reduce airway inflammation and are considered to be the most potent and commonly used first-line anti-inflammatory agents in the treatment of asthma.[24] Corticosteroids (eg, beclomethasone, budesonide, and fluticason) are maintenance therapy for patients with asthma. The anti-inflammatory effect of inhaled corticosteroids is mediated through their binding to corticosteroid receptors, which in turn can affect the transcription of a number of genes.[26]

SNPs located in the promoter region of the GLCCI1 gene have been associated with improved lung function. Other genes such as CA10, CTNNA3 and SGK493 also showed potential effects on response.[27] Several reports on the pharmacogenetics of corticosteroids. It was found that the IL-4 589T allele (589 C/T SNP) was associated with corticosteroid-resistant asthma. For corticosteroid pharmacogenetics, the TBX21 (T-bet) gene (His 33 Gln) and the corticotropin-releasing hormone receptor 1 (CRHR1) gene are relevant. When compared with 33 homozygotes on corticosteroid treatment, TBX21 33 heterozygous individuals/Gln showed a significant increase in airway hyperresponsiveness, especially in Caucasian children.[28,29]

Variations in FBXL7 were found to be associated with altered response to inhaled corticosteroids in children based on self-reported symptoms, but not in adults. GLCCI1 has been identified as a genetic marker associated with improved lung function in corticosteroid use in children.[25]

Leukotriene receptor agonists (LTRA)

Leukotriene receptor agonists (LTRA) may be added if the child's asthma is not well controlled.[11] Leukotriene is an important mediator in asthma, in children than in adults. Eosinophils, mast cells, and alveolar macrophages all produce leukotrienes. Several enzymes are involved in the formation of leukotrienes, including 5-lipoxygenase (ALOX5) and leukotriene C4 synthase (LTC4S). It is a membrane-bound glutathione transferase that converts LTA4 to LTC4 by synthesizing cysteine-leukotrienes.[23]

Leukotriene modifiers exhibit anti-inflammatory activity in asthma, improving control and symptoms with minimal side effects. SNPs located in the LTC4 gene have been associated with responses to montelukast.[30] Patients who

were homozygous for A-444 had a worse FEV1 response to the drug zafirlukast (leukotriene receptor antagonist) than the A/C or C/C genotypes. Furthermore, leukotriene receptor antagonists (montelukast or pranlukast) were more effective in adults and children with genotype A/C or C/C at position-444 (LTC4S-444) compared with genotype A/A.[31,32] Leukotriene modification is thought to mediate bronchoconstriction in asthmatic patients. Leukotriene binds to leukotriene receptors on leukocytes and lung smooth muscle cells.[25]

Pharmacogenomic effects in children are diverse, several pharmacogenomic studies of asthma treatment in various pediatric populations are described in TABLE 1.

TABLE 1. Pharmacogenomic studies on asthma treatment in various pediatric populations

Types of polymorphism	Population (n)	Effect	Reference
Inhaled corticosteroids			
NR3C1 rs41423247 C>G	Turkey (n=82)	Homozygous G allele was associated with a higher increase in FEV1 at 4 h, in children with moderate to severe asthma exacerbations treated with high-dose ICS.	Keskin *et al.*[33]
GLCCI1 rs37972 C>T rs37973 A>G	USA (n=219)	Associated with reduced inflammatory cell apoptosis, resulting in reduced clinical response to inhaled glucocorticoids.	Tantisira *et al.*[34]
GLCCI1 rs37973 A>G	USA (n=1916)	The use of inhaled corticosteroids does not respond to FEV1	Hosking *et al.*[35]
T gene rs1134481 G> T rs2305089 C>T rs3099266 C>T	USA (n=418)	Associated with an unfavorable FEV1 response to the use of inhaled corticosteroids.	Tantisira *et al.*[17]
HCER2 rs28364072 A>G	Netherlands (n=1325)	Associated with an increase in the daily dose of inhaled corticosteroids. Homozygotes of this allele variant had an increased risk of wheezing, shortness of breath, cough in the previous 12 months and asthma-related sleep disturbances. It is also associated with an increased risk of severe exacerbations.	Koster *et al.*[36]e
ORMDL3 rs2872507 G>A	Slovenia (n=311)	Children with atopic asthma with genotype AA when compared with patients with genotypes AG and GG had better treatment outcomes in response to anti asthmatic treatment with inhaled corticosteroids.	Berce *et al.*[37]
VEGFA rs2146323 A>C	Slovenia (n=311)	The response to ICS therapy in asthmatic patients with the AA genotype had a greater increase in % predictive FEV1 compared with the AC or CC genotypes. In contrast, the AA genotype was associated with uncontrolled asthma in patients regularly receiving LTRA therapy and a poorer FEV1/ FVC ratio in patients episodic on LTRA therapy.	Balantic *et al.*[38]

TABLE 1. cont.

Types of polymorphism	Population (n)	Effect	Reference
Leukotriene receptor agonists (LTRA)			
VEGFA rs833058 C>T	Slovenia (n=311)	LTRA therapy used episodically in patients with the TT genotype had a predicted % increase in FEV1, compared with CT or CC genotypes with no improvement in patients.	Balantic *et al.*[38]
ALOX5 promoter SP1	USA African-American (n=270)	Contributes to increased cys LT exposure as determined by urinary LTE4 levels, decreased lung function, and potentially poorer asthma control. The tandem repeat genotype of the ALOX5 SP1 promoter may be a risk factor for worse asthma.	Mougey *et al.*[39]
ALOX5AP rs9551963 C>A	Puerto Rico (n=649)	Only patients with a genotype containing the minor allele showed an increased bronchodilator response to leukotriene modifiers	Tcheurekdjian[40]
LTA4H rs2540491 G>A rs2540487 G>A	Puerto Rico (n=649)	The use of LTRA was associated with a clinically significant increase in the percentage change in FEV1 after albuterol administration.	Tcheurekdjian[40]
SLCO2B1 rs12422149 G>A	USA (n=26)	Associated with lower plasma levels of motelukast	Mougey *et al.* [41]
***β*-agonist**			
ADRB2 rs1042713 G>A	USA (n=544)	Lung function responses were maintained throughout treatment and no statistically significant changes from baseline between genotypes in treatment were observed. There is no evidence of a pharmacogenetic effect of receptor variation on salmeterol response.	Bleecker *et al.*[42]
CRHR2 rS73294475 T>C	USA Latino (n=1782)	Associated with better bronchodilator response	Drake *et al.*[43]
THRB rs892940 G>A	USA (n=607)	Associated with better bronchodilator response	Duan *et al.*[44]

DISCUSSION

The pediatric population is characterized by progressive developmental changes related to the growth and maturation of organs and functions.[45] Pharmacogenomic studies have been carried out in adults, but the results in adults cannot be directly applied to pediatric patients. Pediatric patients are still developing processes and systems (such asmetabolism, hemostasis, and drug biotransformation.[11]

Pharmacogenomic treatment is a genetic test that helps assess and explain the patient's response to treatment, so that it can help make better drug and dose selection.[13] Individual genomic differences can influence drug disposition and effects of many drugs, and identification of biomarkers is critical for adjusting dose and optimizing response.[45]

Genetic variation has been shown to have a role in treatment response to improve asthma management and improve the quality of life of asthma patients. The findings have made it possible to validate the associations of genes previously associated with asthma treatment response (ADRB2, GSDMB, FCER2, VEGFA, SPAT2SL, ASB3, and COL2A1), and identify new associations (PRKG1, DNAH5, IL1RL1, CRISPLD2,

MMP9, APOBEC3B- APOBEC3C, EDDM3B, and BBS9).[27] Asthma is a heterogeneous respiratory disease characterized by chronic airway inflammation, reversible airflow obstruction, and airway hyperresponsiveness. Asthma symptoms include wheezing, dyspnea, chest tightness, and coughing. These symptoms may resolve spontaneously, but most patients require pharmacological treatment to control them. Pharmacotherapy is not always effective, and some patients may experience worsening episodes of the underlying disease situation (exacerbations). These acute episodes are responsible for limiting the patient's daily activities and can lead to disability, the need for intubation, and can even be life-threatening.[27] Diseases such as asthma, autism, ADHD, juvenile rheumatoid arthritis and epilepsy occur during childhood, if not treated with proper treatment there will be ADR which is a significant death in pediatric patient.[14]

According to study conducted by Dahlin *et al.*[46] the result is obtained through the response GWAS montelukast differential in four asthma cohorts. We have identified SNP a significant genome-wide area, rs6475448, which is present in MLLT3. These SNPs may represent a novel mechanism for the differential response to leukotriene-modifying agents in asthma. Genetic variants are known to have a role in the response to asthma treatment with different drugs given that these traits have been shown to be inherited. Identification of variants that affect only one base pair, called SNPs. Candidate gene studies have been performed to identify genetic variants in specific genes previously associated with disease and pharmacological treatment. The GWAS data can be obtained either by genotyping microarrays and through high throughput DNA sequencing. Microarrays used for whole-genome genotyping focus on specific SNPs that represent variations across the genome.[27]

CONCLUSION

Asthma is a chronic inflammatory disease of the airways characterized by bronchial hyper-responsiveness, reversible airflow limitation, and respiratory symptoms. Pharmacogenomics-based treatment can help assess and explain the patient's response to treatment, so that it can help make better drug and dose selection. The purpose of all these implementation programs is to provide optimal, safe, and economical use of drugs for patients receiving these high-risk drugs.

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