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Influence of Genetics Polymorphism of OATP2B1 Transporter on Montelukast Response in Samples of Asthmatic Children

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Abstract

Objectives: The primary objectives are to evaluate the impact of OATP2B1c.935G>A (rs12422149) genetic polymorphisms on montelukast treatment responses in children with asthma in Iraq.

Methods: This observational cross_sectional study was conducted from the beginning of October 2022 up to the ending of September 2023 at the respiratory clinic centre of the Karbalaa Hospital for Children.One hundred participants, both male and female, aged between six and fifteen, who had been taking montelukast as a control medication on a daily basis for at least a month, were included in the study. Following DNA extraction, allele_specific PCR was performed to identify the genotypes of the various patients. Measurements of total serum IgE, the Asthma Control Test (ACT), and the Pulmonary Function Tests (PEF and FEV1) were made.

Results: Genetic amplification results indicate that the distribution of the polymorphism of the c.935G>A gene was 48% in GG wild homozygous, 45% in GA mutant heterozygous, and 7% in mutant homozygous AA. Patients with mutant genes (GA and AA) exhibit high total IgE, low PEF and FEV1, and <19 ACT scores. This polymorphism is expected to have a significant association (P value < 0.05) with montelukast responsiveness.

Conclusions: A significant association, was seen between the montelukast response and the OATP2B1 c.935 G>A genetic polymorphism.

Keywords: Montelukast, asthmatic children, OATP2B1 transporter, leukotrienes modifiers, genetics polymorphism.

Introduction

Childhood asthma is a major global public health issue.It is estimated that 300 million people globally suffer from asthma, and if current trends continue, that figure might reach 400 million before 2025.[1] Asthma ranks within the most prevalent 20 illnesses worldwide in terms of years.[2]

Leukotriene antagonist are available as oral controller drugs for the treatment of pediatrics asthma.[3] They are the best adjuvant therapy in addition to inhaled corticosteroids (ICS) for children with moderate to severe persistent asthma. They can also be used as an alternative to ICS for the treatment of mild persistent asthma.[4] According to Meshram D. et al.,[5] montelukast is aform of cysteinyl leukotriene receptor 1antagonist that is rapidly absorbed when taken orally. Wermth, Badri, et al.,[6] reported that montelukast had a mean oral bioavailability of 64% and a 99% binding to the plasma proteins. Some studies believe that OATP2B1 is expressed on the basolateral membrane of entero-cytes in the intestine and helps with substance absorption into almost all organs. For instant Mooji et al.[7] found that the transporter facilitated the movement of compounds through the enterocyte to blood, but Keiser et al.[8] found that the transport occurred from the blood circulation into the entrocyte.In the study by Mougey et al.,[9] plasma concentrations of montelukast have been linkedto the genetic variation of OATP2B1, rs12422149 (G/A), resulting in in the amino acid R312Q rearrangement. They observed that the homozygotes subjects had a higher plasma concentration than the heterozygotes. Moreover, homozygotes' Asthma Symptom Utility Index scores improve following 1 and 6 months of montelukast therapy in comparison to their baseline levels. So, the rs12422149 may have an effect on the pharmacokinetics and therapeutic response of montelukast.[10] In a follow_up study on teenagers, the same writers validated these results.[11] Nevertheless,nodata supporting the impact associated with SNV rs12422149 on montelukast pharmacokinetic was discovered in two subsequent investigations conducted on healthy participants in White Finnish nor Korean population groups, respectively.[12,13] The main functional consequence of the OAT2B1 c.935G>A mutation has been associated with reduced transport activity; however, this effect appears to be highly reliant on the substrate and laboratory model.[14] There is significant inter-individual variability in the efficiency of montelukast in clinical practice.

The therapeutic response to montelukast was connected with variations in the genes encoding the membrane transporters or metabolising enzymes.[15] The primary goal of this study is to identify the c.935G>A (rs12422149) genotypes in children with asthma from Iraq and assess the impact of these genetic polymorphisms on the individuals' reaction to montelukast.

Patient and Methods

Study Design

This observational cross sectional study was done from the beginning of November 2022 to the end of September 2023, at the respiratory clinic center of Kerbala Teaching Hospital for

children. The study included children who hadmild or moderate asthma who showed persistent symptoms.

Patients Selection

The GINA, asthma control test, as well as pulmonary function test were used to evacuate 100 children with mild to moderate chronic asthma who were regular visitors to the hospital's asthma center. After obtaining written agreement of their parents and filling out a premade questionnaire, children with asthma were selected for this study.

Methods

Samples Collection

The 4 milliliters of venous blood collected from each participant for this study have been separated into two tubes: 2milliliters for the genetic testing and 2 milliliters for the total IgE evaluation.

Assessment of Lung Function (Pulmonary Function Test)

Lung function was assessed using a disposable turbine and Spirometer (Spirolab I), according to American Thoracic Society (ATS).[16]

IgE Assessment

The Uroimmun kit was utilised to perform ELISA in order to determine the total serum IgE level.

Childhood Asthma Control Test C-ACT

The seven_question asthma control exam has a total score that ranges from 0 to 25 based on the sum of the answers to each of the seven items. [17]

Chemicals

Agarose gel powder, TAE Buffer, Absolute Ethanol, DNA ladder, primers, ethidium bromide, nuclease-free water DNA extraction kit and PreMix.

Genotyping of the Single Nucleotide Polymorphisms

OATP2B1 c.935G>A (rs12422149) is the gene that the current study is targeting in children with asthma. Allele specific Polymerase Chain Reaction (AS-PCR) was performed after DNA extraction, and PCR templates were run on an electrophoresis gel for UV light final detection.

Statistics

Following the transfer of research participant data into an electronic database and its subsequent error and inconsistency checking, the data was maintained, processed, and analyzed using IBM's statistical programmer for social sciences (SPSS) version 24, Standard deviation (SD), percentage, and mean were provided as the outcomes. To evaluate group differences, analysis of variance (ANOVA) test outcomes were employed. The student t_test was used to analyse the total IgE level.

The Chi_square test was used to look at the variations in data supplied by percent (>5) among genotype groups. Investigating differences in data expressed as percents (%) was done using the analysis of variance. Fisher's exact values were done for above 5 cells numbers. For all statistical tests, only a *P*-value of less than 0.05 considered significant.

Results

This study included one hundred children ranging in age from six to fifteen. Males made up the majority of them (64%) while the male to female ratio was 1.7:1. A month prior to the research, every patient had been taking montelukast on a regular basis. Patients had a body mass index (BMI) of 17.8 ± 4.87. Group 1's total serum IgE level (years 6–9) was 191.57 ± 21.46, which was higher than normal (155 IU/ml), and Group 2's total serum IgE level (ages 10–15) was 208.43 ± 27.59, which was also higher than normal (199 IU/ml). Table 1 lists the asthma control tools, such as ACT and PFT parameters.

Results were expressed as mean ± SD. FEV1: force expiratory volume in 1 second PEF: Peak Expiration force.

The following Figure 1 display the distribution of the genetic polymorphism of SLCO2B1 c.935G>A (rs12422149) in children with asthma.

Ages, genders, and BMI did not significantly correlate with the SLCO2B1 c.935G>A (rs12422149) genetics polymorphism, but total igE, AST, and PFT(FEV1 and PEF) did significantly correlate with this polymorphism.

The Table 2 provides a summary of these associations' specifics.

Table 1. **Asthma control tools of studied patients**

Asthma control tools in children (*n* = 100)		
Data presented by percent (%)		
Asthma control test score	Controlled (20–25) Partly controlled (16–19) Poorly controlled (5–15)	21 39 40
	PFT in Asthmatic children (n = 100)	
Pulmonary function Parameters	Mean ± SD	Normal values
FEV1 (L)	81.16 ± 12.29	>80
PEF (L/S)	78.78 ± 12.92	>80

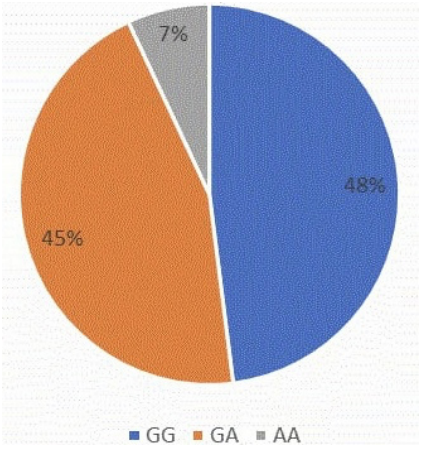

Fig. 1 **Percent distribution of different genotype of SLCO2B1 transporter in asthmatic children.**

Table 2. **Associations between SLCO2B1 c.935G>A with clinical parameters in asthmatic children on montelukast therapy**

Parameters	Genotypes	*N* = 100	Mean ± SD	*P* values
Total serum IgE	GG	22	67.36 ± 53.4	
Group 1 (ages 6–9)	GA	21	251.8 ± 3.24	0.001
N = 46	AA	3	131.38 ± 1.74	
Group 2 (ages10–15)	GG	26	87.02 ± 69.34	0.007
N = 54	GA	24	315.26 ± 2.94	
	AA	4	304.99 ± 5.95	
Genotypes	GG	GA	AA	*P* value
AST				
Well controlled (20–25)	17	4	0	0.003
Partly controlled (19–16)	20	16	3	
Un controlled (15–0)	11	25	4	
PFT	(*n* = 48)	(*n* = 45)	(*n* = 7)	
FEV1 (L)	82.37 ± 12.37	81.86 ± 11.5	68.28 ± 9.62	0.014
PEF (L/S)	81.08 ± 11.97	78 ± 13.8	68 ± 6.21	0.036

Discussion

Research indicates that people with varied cultural and ethnic backgrounds respond differently to medications.This is most likely caused by genetic changes that are inherited from a specific ancestry and are linked to the intensity of the condition or degree to which an individual reacts totreatment.[18] Pharmacogenomics studies the relationship between drug reactions and genetic variation.[19]

In early childhood, boys are reported to be more susceptible than girls to have symptoms of asthma; however, by mid-adolescence, the burden is almost evenly reduced and starts to favour girls.[20–22] The 64% of the participants in the current study were boys, which is in line with findings from earlier studies done in Iraq,[23,24] which also revealed that male are more likely than female to be involved in specific communities. If an individual's ACT score remained higher than 20, they were deemed to have managed their asthma during the course of this trial. Only 21% of the subjects had a disease under control, whereas 41% had an illness that was only partially under control (>16) as shown in Table 1. This study's results are in contrast to a research project conducted in Riyadh.[25] In that study, 67.19% of the children who participated had controlled asthma. Patients were classified of having controlled asthma if their AST score was greater than 19. Furthermore, only 32.81% of them were thought to have an uncontrollable medical condition. This study used 64 children as its sample. Our findings are consistent with a study by Ungar et al.,[26] on 879 children with asthma between the ages of 1 and 18, in which only 11% of individuals had asthma under control. Patients were classified as having controlled asthma if their ACT score was still above 19. Children that take part in the trial have controlled asthma. Furthermore, only 32.81% of them were thought to have an uncontrollable medical condition. This study used 64 children as its sample.

Genetic polymorphism was distributed as follows: 48% in wild homozygous GG, 45% in heteroz_ygous GA, and 7% in mutant homozygous AA individuals.Comparable results were obtained by Li Qian, et al.,[15] who studied a sample of 50 Chinese people and discovered that the allele of c.935G>A was present in this group at a frequency of 42% for GG, 48% in GA, and 10% for AAThe allele frequencies of 227 healthy, unrelated male and female Korean volunteers were found to be 31% GG, 51% GA, and 17% AA in another study.[27] These results are similarly consistent with the current investigations conducted on the Iraqi population. The alleles distribution was different in Finnish Caucasian volunteers; 86.4% for GG, 13.6% for GA, and AA not observed.[28]

According to this study, ACT scores and the genetics polymorphism of the gene c.935G>A are significantly, correlated. Table 2 demonstrate the substantial differences between the genotype groups. Individuals with GG genotypes exhibit superior AST findings in comparison to those with GA and AA genotypes. Uncontrolled asthma is still incredibly frequent, even with the wealth of effective treatments available.[29] During a recent 4_week period, the montelukast group had supe_rior asthma control, as evidenced by a lower percentage of asthmatic children who experienced difficulties more than twice a week, woke up or coughed at night, or required relief treatment more than twice a week. This research compared montelukast and low_dose budesonide inhalersfor treating paediatrics with moderate asthma. Additionally, the montelukast group had fewer people with an ACT/C_ACT score of less than 19.[30]

Individuals with mild persistent asthma are those who have symptoms of asthma at least twice a week, but not more than once a day. If a patient has both a PEF and a FEV1 greater than 80%, they are labelled with mild persistentasthma after the age of five. Patients older than five who meet the qualifying factors of 20_30% and have a PEF and FEV1 > 80% are diagnosed with mild persistent asthma. Individuals who have daily asthma symptoms that are aggravated by exercise are considered to have moderate persistent_asthma. A PEF or FEV1 that is between 60% and 80% of anticipated values and with a variability of more than 30% is indicative of moderate persistent asthma in patients older than 5 years old.[31] In numerous studies, montelukast was shown to improve pulmonary function (an average of FEV1 values improved by 68% and more) and significantly reduce asthma symptoms, including the percentage of days without requiring rescue.[32] Children using montelukast for four weeks, either as monotherapy or in conjunction with budesonide, demonstrated an increase in FEF25_75% values, per the research conducted by Stelmach I. et al.,[33] Also demonstrates that whereas inhaled drugs never

get to the lower respiratory tract, systemic drugs_like oral montelukast_can since inflammation in the airways is a major factor in the occurrence of asthma. Another study by Nieto et al.,[34] discovered that while montelukast had no effect on the PEF 25–75%, it had a favorable effect on the children's small airway as measured by impulse oscillometry.

Several studies have demonstrated a correlation between total IgE levels and the severity of asthma in both adults and children, with serum IgE levels rising withhigher asthma severity.[35–37] As indicated in Table 2, there were significant associations between the total blood IgE level and the polymorphism in genes c.935G>A. High total IgE levels were also seen in asthmatic patients receiving control therapy in a study by Qu X et al.,[38] who reported that the IgE level in asthmatic patients receiving treatment was noticeably greater than that in asthmatic controls. Another study reported that the blood IgE levels in asthmatic individuals were only reduced by high dosages of ICSs and montelukast.[39] According to the current study, patients with the GG genotype have PEF and FEV1 values that arenearly normal, while patients with the GA or AA genotypes have values that are below normal Table 2. Furthermore, there is a statistically significant difference between the three genotype groups.

Conclusion

SLCO2B1 transporter genetic variation may have an impact on how well asthmatic children respond to montelukast therapy. The GG genotype participants improve more than the AA and GA genotype subjects in the terms of lung function (FEV1, PEF), AST, and seum total IgE level following montelukast therapy. Additional research with a bigger sample size is necessary to validate the results.

Recommendation for Future Works

1. Taking into account different gene polymorphisms related to montelukast and/or researching other medications used to treat paediatric asthma.
2. A case-control cohort study with a bigger sample size that looks at the same genes or other associated genes.

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