Influence of Leukotriene Pathway Polymorphism on Responsiveness to Montelukast, Budesonide Plus Formoterol in Patients with Asthma

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Abstract:

Variability between patients in response to montelukast, and budesonide / formoterol inhalation powder may be related to genetic variation and non-genetic factors. this paper aims to determine association between polymorphism in leukotriene pathway candidate gene with lung function outcomes in Iraqi patients with asthma receiving montelukast, budesonide plus formoterol inhaler in comparison with healthy control. This research was done on a study group of 80 Baghdad-based Iraqi patients. 40 asthmatic patients receiving montelukast were in the first group, while 40 asthmatic patients on budesonide / formoterol inhalation powder (160/4.5mcg/dose) were in the second group. Screening for the presence of ALOX5 rs2115819, LTA4H rs2660845 and CysLTR1 rs320995 SNPs allelic variants genes were determined using conventional PCR technique and sequencing. In montelukast group, the % change in FEV1 in patients with the GG genotype for ALOX5 (rs2115819) SNP were significantly improved after montelukast intake compared with those carrying AA or AG genotypes. For budesonide / formoterol inhalation powder patients group, the included polymorphism had no significant association with the %change in FEV1. As a conclusion Asthmatic patients carrying AA genotype for ALOX5 rs2115819 may not achieved the optimal response to montelukast treatment. Budesonide / formoterol inhalation powder cannot be used effectively in patients with ALOX5 rs2115819 polymorphism.

Keywords: Asthma, Montelukast, ALOX5 SNP, Budesonide / Formoterol Inhalation Powder, Polymorphisms

1. Introduction:

Asthma defines as a chronic inflammatory disease of the airways in which many types of cells play a role especially mast cells, neutrophils, eosinophils, macrophages, T lymphocytes and epithelial cells. In vulnerable individuals, this inflammation causes recurrent episodes of coughing (especially at night or early in the morning), shortness of breath, wheezing and chest tightness (GINA, 2021). Leukotrienes (LTs) are derived from arachidonic acid (AA). Leukotriene (LTs) are inflammatory mediators that play important role in both normal host defense and in inflammatory diseases like asthma, these cells, in turn, cause the smooth muscle contraction and airway tightening in asthma (Gauvreau et al., 2015).

Arachidonic acid is metabolized by ALOX5 and 5-lipoxygenase activating protein into 5-hydroperoxyeicosatetraenoic acid and LTA4. LTA4 hydrolase (LTA4H) transforms LTA4 into LTB4, and LTC4 synthase combines reduced glutathione with LTA4

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to create LTC4. By means of glutamyltransferase and dipeptidase, LTC4 is transformed into LTD4 and LTE4 (Woods et al., 1993). Asthma symptoms mediated by the cysLT1 receptor and brought on by cysLTs (Drazen and Austen, 1987).

2. Materials and Methods:

2.1 Chemicals

TAE Buffer (50x), Absolute Ethyl Alcohol (99.9%), Loading dye, 100bp DNA ladder, and Free Nuclease Water

2.2 Study Design and Patient Studies

This is an interventional study, which was conducted on a sample group of Iraqi asthmatic patients from Baghdad with Arabic race. In this study, 80 adults asthmatic patients (male and female) aged 18 to 60 years were divided into two groups, first group involved 40 patients were receive montelukast 10 mg once daily at night for 4 weeks. 40 patients in the second group received budesonide / formoterol inhalation powder twice daily for 4 weeks. Before participating in the study, each patient answered questions about their demographics, smoking history, age at which their asthma first manifested, medical history, and whether or not they had used long-acting beta agonists or anti-leukotriene medications two months prior to the lung function test.

2.3 Genomic analysis of the single nucleotide polymorphisms

In this investigation, we focused on the ALOX5 gene's rs2115819. All participants in this pharmacogenetic investigation provided DNA for collection. Macrogen Corporation of South Korea supplied a PCR product for Sanger sequencing.

2.4 Outcomes

The following results were used to examine associations between genetic variants:

Patients with ALOX5rs(2115819) carrying the homozygous mutant genotype (GG) demonstrated higher percentage of FEV1 change (125.41 ± 24.62) than either those carrying AA or AG genotypes (35.31 ± 12.7, 63.0 ± 14.2 respectively) with significant differences. Patients with LTA4H (rs2660845) carrying the homozygous mutant genotype (AA) demonstrated higher percentage of FEV1 change (85.54±16.9) than either those carrying AGor GG genotypes (45.03 ± 13.25, 42.35 ± 12.69 respectively) with significant differences. Patients with CysLTR1 (rs320995) carrying the homozygous mutant genotype (CC) demonstrated higher percentage of FEV1 change (88.3 ± 15.24) than either those carrying TT or TC genotypes (50.92 ± 9.56, 41.73 ± 10.0 respectively) without significant differences.

2.5 Statistics

Data tabulation and coding performed via Microsoft Excel-2013. Descriptive and analytic statistics done using SPSS V24 software statistical program. It was as follow:

- The descriptive statistics included mean ± standard deviation (S.D) for measurable variables.
- P-values < 0.05 were taken to indicate statistically significant differences and < 0.01 highly significance.

3. Results:

3.1 Montelukast

Patients carrying the homozygous mutant genotype (GG) demonstrated higher percentage of FEV1 change (125.41 ± 24.62) than either those carrying AA or AG genotypes (35.31 ± 12.7 and 63.0 ± 14.2, respectively) with significant differences as shown in Table 1 and Figure 1.

Table 1. Association of different genotypes of rs2115819, rs2660845 and rs320995 polymorphisms with patient's forced expiratory volume in one second (FEV1) after taking montelukast

Polymorphisms	Genotypes	% change in FEV1	*P*-value
ALOX5 rs2115819	AA	35.31±12.7	0.001
	AG	63.0±14.2	
	GG	125.41±24.62	
LTA4H rs2660845	AA	85.54±16.9	0.035
	AG	45.03±13.25	
	GG	42.35±12.69	

CysLTR1 rs320995	TT	50.92±9.56	0.123
	TC	41.73±10.0	
	CC	88.3±15.24	

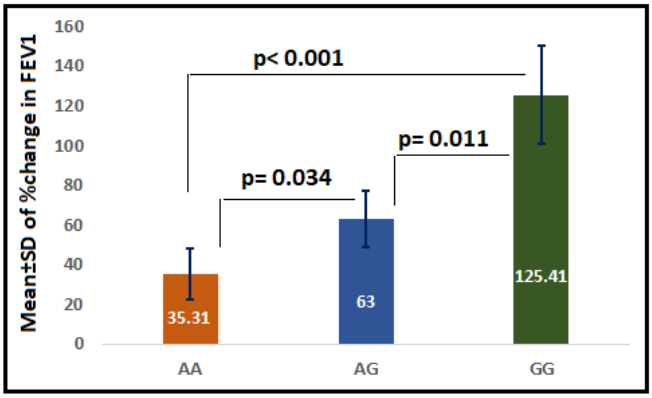

Fig. 1. Association of different genotypes of rs2115819 polymorphism with the % change in forced expiratory volume in 1 second (FEV1) in patients treated with montelukast

Likewise, Regarding, patients carrying AA genotype of the LTA4H rs320995 polymorphism had higher FEV1 change (85.54 ± 16.9) than those carrying AG or GG genotypes (45.03 ± 13.25 and 42.35 ± 12.69, respectively) with significant differences as shown in Figure 2.

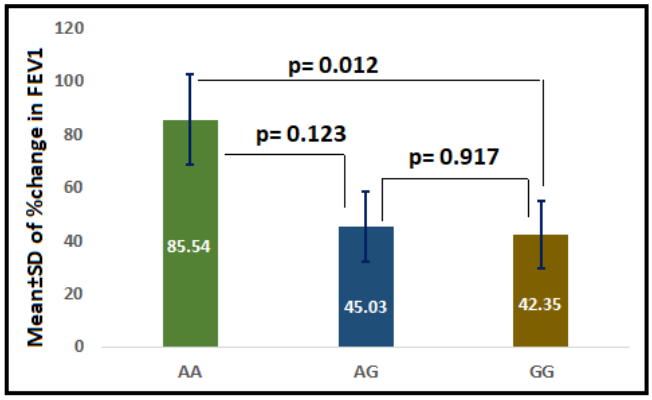

Fig. 2. Association of different genotypes of rs2660845 polymorphism with the% change in forced expiratory volume in 1 second (FEV1) in patients treated with montelukast

Although patients carrying CC genotype of CysLTR1rs320995 polymorphism associated with higher % change in FEV1 (50.92 ± 9.56) than those carrying TT genotype (41.73 ± 10.0) or TC genotype (88.3 ± 15.24), the differences were not significant as seen in Figure 3.

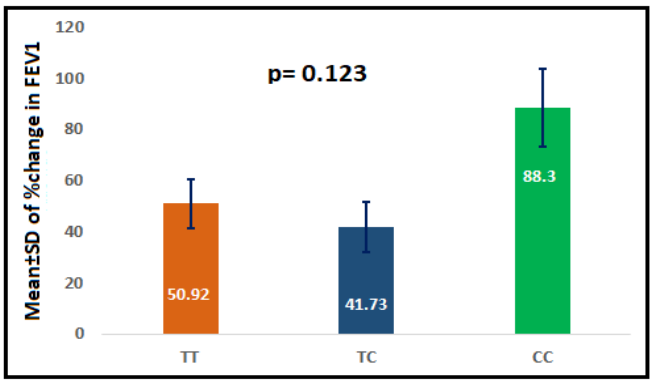

Fig. 3. Association of different genotypes of rs320995 polymorphism with the % change in forced expiratory volume in 1 second (FEV1) in patients treated with montelukast

3.2 Budesonide / Formoterol Inhalation Powder

For this combination, carriers of different genotypes of the three included polymorphism had comparable values of % change in FEV1 (despite the presence of some variation) with no significant differences as shown in Table 1 and Figures 4 to 6.

Table 2. Association of different genotypes of rs2115819, rs2660845 and rs320995 polymorphisms with the forced expiratory volume in 1 second (FEV1) in patients treated with budesonide/ fermoterol inhalation powder

Polymorphisms	Genotypes	% change in FEV1	*P*-value
ALOX5 rs2115819	AA	23.12 ± 7.5	0.651
	AG	17.24 ± 7.62	
	GG	8.7 ± 1.2	
LTA4H rs2660845	AA	11.15 ± 5.16	0.458
	AG	23.38 ± 11.2	
	GG	13.07 ± 2.2	
CysLTR1 rs320995	TT	24.3 ± 13.45	0.372
	TC	9.76 ± 3.7	
	CC	11.6 ± 5.7	

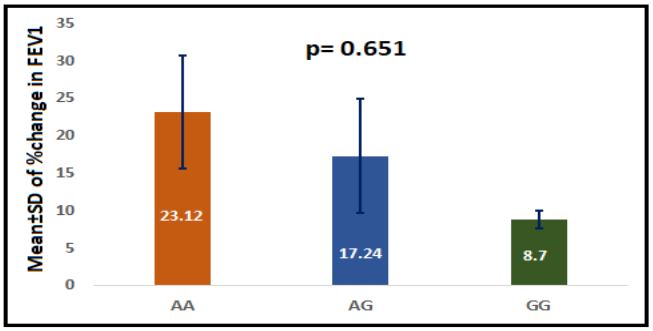

Fig. 4. Association of different genotypes of rs2115819 polymorphism with the forced expiratory volume in 1 second (FEV1) in patients treated with budesonide/formoterol inhalation powder

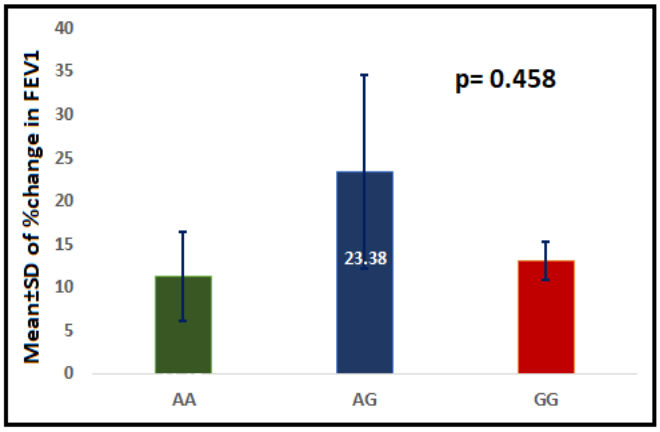

Fig. 5. Association of different genotypes of rs2660845 polymorphism with the forced expiratory volume in 1 second (FEV1) in patients treated with budesonide/formoterol inhalation powder

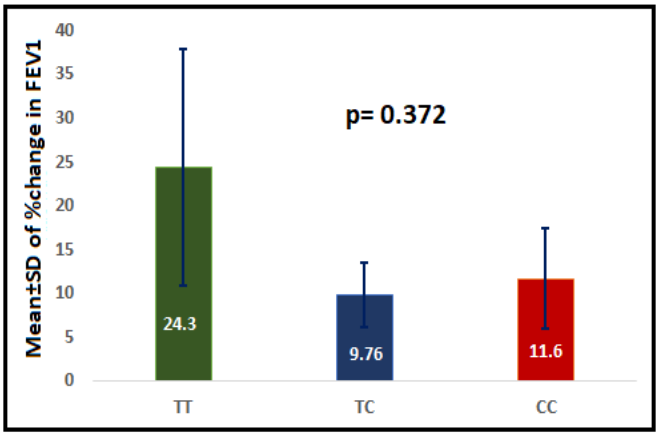

Fig. 6. Association of different genotypes of rs320995 polymorphism with the forced expiratory volume in 1 second (FEV1) in patients treated with budesonide/formoterol inhalation powder

4. Discussion:

Association of rs2115819, rs2660845 and rs320995 polymorphisms with drugs responsiveness

4.1 Montelukast

In the present study, for ALOX5 SNP, patients carrying the homozygous mutant genotype (GG) demonstrated improvement in % change FEV1 than either those carrying AA or AG genotypes after montelukast intake for 4 weeks with significant differences. This finding is in line with result reported previously for the same SNP by Lima et al. (2006) who using DNA from 61 non-Hispanic White American participants with poorly controlled, mild to moderate persistent asthma randomized to treatment with montelukast. According to the latter study, GG genotypes for the ALOX5 SNP considerably outperformed AA and AG genotypes in terms of their FEV1 response to montelukast at 6 months of treatment: 30% (95% CI = −0.017 to 1.21) versus 4.4% (95% CI, −0.025 to 0.66) in AA and 2.0% (95% CI, 0.013–0.075) in AG genotypes.

However, in study done by Kotani et al. (2012) there was no significant association between the GG homozygotes (n=14) of the ALOX5 SNP (rs2115819) and A allele carriers (AA+AG) (n=7) with changes in FEV1 values in Japanese patients (n=21).

Patients carrying AA genotype of the LTA4H rs320995 polymorphism had higher FEV1 change than those carrying AG or GG genotypes after treatment with montelukast for 4 weeks. This result is in accordance with study done by Kotani et al. (2012) who reported a significant association between AA genotype(n=4) of the LTA4H SNP (rs2660845) and changes in FEV1 compared to G allele(GG+GA) carriers. While in a study by Lima et al. (2006), LTA4H (rs2660845) SNP has been shown to effect montelukast response through the prevention of asthma exacerbations with no influence on lung function outcomes.

The result of the present study for CysLTR1 rs320995 polymorphism revealed no significant differences among patients with CC, TT and TC genotypes. results from Lima et al. (2006) study revealed no association between genotypes of the CysLTR1 (rs 320995) gene and changes in FEV1, or asthma exacerbation rates after montelukast treatment.

4.2 Budesonide/Formoterol inhalation powder

In this drug group, although a variations is observed in % change in FEV1 values with ALOX5 rs2115819, LTA4H rs2660845 and CysLTR1 rs320995 SNPs but non-significant difference noticed with any of these three SNPs after 4 weeks of budesonide/formoterol inhalation powder. These results were consistence with a result reported by a study done by Lima et al. (2006) who found that there were no associations between ALOX5, LTA4H and CysLTR1 genotypes and changes in % FEV1 but with placebo. This drug effects were associated with variants in other genes contribute to bronchodilator response heterogeneity (Kotani et al., 2012). A

previous study showed no statistically significant genetic associations were identified between candidate genetic variants and ICS response in patients with asthma (Mougey et al., 2013).

5. Conclusions:

- Asthmatic patients carrying AA genotype for ALOX5 rs2115819 and/or the GG genotype of LTA4H rs320995 polymorphisms may not achieved the optimal response to montelukast treatment.
- Non-significant difference noticed with any of the ALOX5 rs2115819, LTA4H rs320995, CysLTR1 rs320995 SNPs after 4 weeks of budesonide / formoterol inhalation powder.

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