



CysLTR1 promoter polymorphism and requirement for leukotriene receptor antagonist in aspirin-intolerant asthma patients

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Objectives: Leukotriene receptor antagonists (LTRA), such as montelukast, have been used as a first-line treatment for patients with aspirin-intolerant asthma (AIA). This study evaluated associations between the clinical requirement for LTRA and genetic polymorphisms of the *ALOX5*, *LTC4S*, *COX-2*, *CysLTR1* and *TBXA2R* genes in the arachidonic acid cascade in the long-term management of 89 AIA patients from a Korean population.

Methods: Asthma control status was monitored for 1 year with maintenance medications of inhaled corticosteroid and oral LTRA, and AIA patients were classified into three groups according to the mean montelukast dose required per month to maintain asthma control for 1 year: group I (≥ 200 mg montelukast/month; $n = 37$), group II (5–150 mg/month; $n = 25$) and group III (< 5 mg/month; $n = 27$). Genetic polymorphisms in the arachidonic acid cascade were determined using a single-base extension method. **Results:** We found that there was a significant difference in the genotype frequency of the CysLTR1 promoter polymorphism -634C > T among the three groups ($p = 0.007$ for group I vs group II, $p = 0.017$ for group I vs group III), while there were no significant associations between LTRA requirements and polymorphisms of the other genes. The patients with the variant genotype (CT or TT) of the -634C = T CysLTR1 promoter polymorphism showed a higher expression level than those with the common genotype (CC). **Conclusion:** These findings indicate that the CysLTR1 promoter polymorphism is a useful genetic marker for predicting LTRA requirements in the long-term management of AIA patients.

Aspirin-intolerant asthma (AIA) is characterized by the triad of aspirin hypersensitivity, bronchial asthma and chronic rhinosinusitis, often with nasal polyposis [1,2]. Although its pathogenic mechanisms are not fully understood, chronic overproduction of cysteinyl leukotriene (CysLT) is a consistent finding in AIA patients [3]. For many years, the leukotriene C4 synthase (*LTC4S*) gene polymorphism has been one of the key findings to explain the overproduction of leukotriene in AIA [4,5]. Other studies have demonstrated that arachidonate 5-lipoxygenase (*ALOX5*) also contributes to overproduction of leukotriene and susceptibility to asthma [6,7].

We investigated the genetic polymorphisms of genes involved in arachidonic acid metabolism in a larger cohort of Korean AIA patients and discovered several SNPs conferring susceptibility to AIA [8–12]. The GCGA haplotype of four SNPs (-1708G = A, 21C = T, 270G = A and 1728G = A) of the *ALOX5* gene may be involved in AIA development [8] and the *ALOX5* promoter polymorphism, consisting of a variable number of tandem repeats of GC-rich motifs, may be associated with the severity of airway hyper-responsiveness to methacholine in AIA patients [9]. The thromboxane A2 receptor

(*TBXA2R*) 795T > C polymorphism may increase the bronchoconstrictive response to aspirin, leading to the development of the AIA phenotype [10]. The recent novel finding was that cysteinyl leukotriene receptor 1 (*CysLTR1*) promoter polymorphisms were a prominent risk factor for AIA development [11]. By contrast, two promoter polymorphisms of the *LTC4S* gene were not associated with the AIA phenotype [12].

In the management of AIA patients, leukotriene receptor antagonists (LTRAs) are considered effective for symptom control and may block aspirin-induced bronchoconstriction in AIA patients [13,14]. LTRAs have dual therapeutic roles as anti-inflammatory agents and bronchodilators by antagonizing the proinflammatory activities of CysLT and the CysLT-induced smooth-muscle bronchoconstriction [15]. Moreover, the addition of a second-line controller with LTRAs might reduce the dose of inhaled corticosteroid [16]. Given its therapeutic role, the *CysLTR1* gene is considered a promising candidate gene in the pathogenesis of AIA. A recent investigation of genetic polymorphisms of *CysLTR1* suggested that *CysLTR1* promoter polymorphisms confer the genetic susceptibility to AIA by increasing the level of CysLTR1 expression in the asthmatic

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airway [11]. Overexpression of the cysteinyl leukotriene receptor 1 on inflammatory cells was noted in the nasal mucosal cells of chronic rhinosinusitis combined in AIA patients [17].

Several pharmacogenetic studies [18–24] have examined the ability to predict the therapeutic response to LTRA and other LT modifiers in asthmatics. Most of them observed the short-term clinical response in mild-to-moderate asthma patients, focusing on genetic polymorphisms of *LTC4S* (-444A = C) and *ALOX5* (tandem repeat of GC-rich motifs). No pharmacogenetic studies of arachidonate 5-lipoxygenase-activating protein (*ALOX5AP*), *CysLTR1*, *TBXA2R*, prostaglandin-endoperoxide synthase 2 or cyclooxygenase 2 (*COX-2*) have been reported. By contrast, *HLA DPB1*0301* may be a useful marker for predicting the LTRA response in a 1-year follow-up study [25].

Our study assessed the association of the clinical requirement for LTRA with genetic polymorphisms of the *ALOX5*, *ALOX5AP*, *LTC4S*, *COX-2*, *CysLTR1* and *TBXA2R* arachidonate-related genes over 1 year in a large group of AIA patients.

Materials & methods

Subjects & study design

We enrolled 89 South Korean patients (33 males) with mild-to-moderate persistent asthma (90% moderate persistent type) with aspirin sensitivity. The AIA phenotype was defined as patients having a proven history of asthma aggravation on exposure to aspirin/NSAIDs and a positive response (fall in forced expiratory volume in 1 s [FEV1] = 20%) in a lysine–aspirin bronchoprovocation test. The phenotype of asthma was defined as patients having typical asthmatic symptoms including airway hyperresponsiveness to methacholine and reversible airway obstruction. In accordance with the Global Initiative for Asthma (GINA) guidelines (updated 2004), the asthma control state was defined as ‘control of the disease with minimal asthma symptoms’ with near-normal peak expiratory flow (PEF), above 80% of predicted FEV1 value and less than 20% diurnal variability. The requirement for LTRA therapy to maintain the asthma control state was assessed as the mean aggregate dose of montelukast per month taken during the study period by each patient. The pharmacogenetic study was performed as follows: all subjects received an inhaled glucocorticoid (budesonide, 800 µg/day) regularly with a short-acting β₂-agonist as required for

1 year. For the first 2 months, all subjects received oral montelukast (10 mg/day). If asthma symptom control was not achieved within this time, in which uncontrolled asthma was defined as the asthma state with worsening of asthma symptoms including presence of daily and nocturnal symptoms with less than 80% of predicted FEV1 value and more than 20% diurnal variability, the patient stopped receiving montelukast, and other asthma medications were added to achieve control. Such subjects were defined as group III (montelukast requirement of <5 mg/month), in which they do not respond to montelukast well, but do not belong to the severe asthma group. The remaining patients with good control in the first 2 months continued receiving oral montelukast at the same dosage for the subsequent 4 months. At the end of this period, montelukast was withdrawn, and results were followed every week. Those patients whose asthma control decreased (worse asthmatic symptoms and changes in lung parameters: ≥20% PEF rate variability or ≥10% decrease in FEV1) within 1 month of withdrawal were again treated with oral montelukast at the same dosage to achieve best asthma control until the end of the 1-year study (group I, montelukast requirement of ≥200 mg/month; they may also be called the montelukast dependent group, to control asthmatic symptoms). The remainder, whose asthma control was maintained after montelukast withdrawal, was defined as group II (montelukast requirement of 5–150 mg/month). To confirm the patients’ adherence, we did check at every visit whether they took the medications regularly, and the frequency of short-acting β₂ agonist used. Skin prick tests were performed using 12 common aeroallergens (Bencard UK, Bradford, UK), as well as positive (histamine) and negative (saline) controls. Atopy was defined as one or more positive reactions on the skin-prick test results. The study protocol was approved by the institutional review board of Ajou University Hospital, Suwon, Korea and all subjects were fully aware of the scope of this study and signed an informed consent form.

SNP genotyping

A total of 16 SNPs in six genes encoding proteins of the arachidonic acid cascade were genotyped using the SNaPshot ddNTP primer extension kit (Applied Biosystems, CA, USA), as recommended by the manufacturer, using the described extension probes [8–12]. As the three SNPs of *CysLTR1*

(-634C = T, -475A = C and -336A = G) were in perfect linkage disequilibrium with each other, we genotyped the -634C = T as a tagging SNP of three promoter polymorphisms [11].

Real-time PCR of the CysLTR1 gene

Peripheral blood samples (10 H) were collected from ten AIA subjects. Peripheral blood mononuclear cells (PBMCs) were isolated from the blood using Ficoll-Paque Plus (Amersham Biosciences, Uppsala, Sweden) density gradient centrifugation. As PBMCs were collected in an infection-free state, the leukocyte counts were similar. Total RNA was isolated from peripheral blood mononuclear cells using an easy-BLUE Total RNA Extraction Kit (iNtRON Biotechnologies, Seoul, Korea) using the supplier's method. Total RNA (2 µg) was reverse transcribed using an oligo-dT primer and moloney murine leukemia virus (M-MLV) reverse transcriptase (Promega, WI, USA) in a volume of 20 µl at 42°C for 90 min. A total of 25 ng of cDNA was subjected to real-time PCR analysis using SYBR Green I (Molecular Probes, OR, USA) and 2 pmol of gene-specific primers (forward: 5'-TGACCGCTGCCTTTTGTAGTC-3', reverse: 5'-GAGAGGGTCAAAGCAACAATTG-3') in a total volume of 20 µl. PCR was performed on an Applied Biosystems 7500 Real-Time PCR System with an initial 5 min at 94°C, followed by 35 cycles of 30 s at 94°C, 30 s at 60°C and 30 s at 72°C. *CysLTR1* mRNA expression was normalized against β -actin mRNA. The mRNA level of *CysLTR1* gene was compared according to the *CysLTR1* genotype.

Statistical analysis

Statistical analysis was conducted using SPSS version 10 (SPSS, Chicago, IL, USA) and a two-sided p-value = 0.05 was considered significant. Differences among the three groups according to genetic polymorphisms were tested using the χ^2 test. Differences in the mean value of the phenotypic characteristics within AIA patients were compared using analysis of variance and the t-test. As the *CysLTR1* gene is on the X chromosome, the distribution of the *CysLTR1* promoter genotypes were hemizygous within male control subjects, and deviated from Hardy-Weinberg equilibrium ($p = 0.01$). The mean expression level of the *CysLTR1* gene according to the promoter polymorphism was assessed using the Mann-Whitney U-test.

Results

The study subjects were stratified by the requirement for LTRA therapy to control the asthma symptoms and are summarized in Table 1. Between group I and group III, significant differences were noted in baseline FEV1 values ($p = 0.025$), airway hyper-responsiveness to methacholine ($p = 0.011$) and the presence of rhinosinusitis ($p = 0.042$). The AIA patients in group I had more severe asthma symptoms and a greater prevalence of rhinosinusitis than those in group III. In comparing group I with group II, the AIA patients in group I had a higher frequency of atopy and higher serum total IgE levels than those in group II.

A total of 16 genetic polymorphisms of the arachidonate-related *ALOX5*, *ALOX5AP*, *CysLTR1*, *LTC4S*, *TBXA2R* and *COX-2* genes

Table 1. Comparisons of the clinical parameters in three study groups within aspirin-intolerant asthma.

	Group I: ≥ 200 mg/ month (n = 37)	Group II: 5–150 mg/ month (n = 25)	Group III: < 5 mg/ month (n = 27)	p-value	
				Group I vs Group II	Group I vs Group III
Age (years)	44.2 $\pm$ 11.9	49.2 $\pm$ 11.6	40.1 $\pm$ 14.1	0.112	0.213
Sex (Female)	30/37 (81.1%)	12/25 (48.0%)	14/27 (51.2%)	0.012	0.016
Atopy (presence)	23/37 (62.2%)	7/25 (28.0%)	15/27 (55.6%)	0.011	0.616
Asthma duration (year)	7.3 $\pm$ 6.7	7.8 $\pm$ 5.8	7.0 $\pm$ 5.0	0.786	0.840
Log serum total IgE (IU/ml)	2.3 $\pm$ 0.6	2.0 $\pm$ 0.5	2.1 $\pm$ 0.6	0.046	0.314
Baseline FEV1 (%)	81.4 $\pm$ 21.0	75.7 $\pm$ 27.9	93.3 $\pm$ 20.0	0.368	0.025
Methacholine PC20 (mg/ml)	1.1 $\pm$ 1.2	3.2 $\pm$ 7.5	8.5 $\pm$ 11.4	0.254	0.011
Rhinosinusitis (+/-)	34/37 (91.9%)	18/25 (72.0%)	19/27 (70.4%)	0.074	0.042
Nasal polyp (+/-)	21/37 (56.8%)	12/25 (48.0%)	12/27 (44.4%)	0.606	0.448

FEV1: Forced expiratory volume in 1 s.

were investigated to evaluate any association with the LTRA requirement in AIA patients (Table 2). The frequency of the variant genotype of the *CysLTR1* -634C > T promoter polymorphism was significantly higher in group I (78.4%) than in group II (44.0%, $p = 0.007$) or group III (48.1%, $p = 0.017$). The frequency of the variant genotype of the *CysLTR1*+927T > C polymorphism was also significantly ($p = 0.016$) higher with group I (68.6%) than in group II (34.8%), but this was not significant compared with group III (41.7%, $p = 0.060$). In addition, minor allele frequencies of two *CysLTR1* polymorphism in group I were significantly higher than those in group II and group III ($p = 0.05$, respectively). By contrast, no significant associations were noted in the study subjects between the other 14 SNPs of *ALOX5*, *ALOX5AP*, *LTC4S*, *TBXA2R*, and *COX-2* and the LTRA requirement (all $p = 0.05$).

The *CysLTR1* mRNA level in patients with the -634C > T variant genotypes (CT or TT) tended to be higher than those with the CC genotypes although the p -value was not significant (Figure 1).

Discussion

LTRAs, such as zafirlukast and montelukast, improve lung function in more than 50% of asthmatics, including the FEV1 and PEF [15]. LTRAs are used to manage AIA patients as persistent production of CysLT is a prominent feature of patients with AIA [14, 26].

In this study, when the AIA patients were stratified by the requirement for LTRA, the AIA patients in group I showed more severe clinical characteristics, including a lower baseline FEV1, greater airway responsiveness to methacholine, and higher prevalence of rhinosinusitis compared with those in group III (Table 1). These findings suggest that the AIA patients with presenting with the typical features of Samter's triad (bronchial asthma, nasal polyps and aspirin sensitivity) may require persistent use of LTRAs to control their asthma symptoms.

Most pharmacogenetic studies for LTRA responses have been focused on leukotriene-related genes, because the chronic production of CysLT may be attributable to abnormalities of arachidonate-related genes. To investigate whether genetic polymorphisms of arachidonate-related genes are associated with the LTRA requirement, we examined 16 genetic polymorphisms of the arachidonate-related *ALOX5*, *ALOX5AP*, *CysLTR1*, *LTC4S*, *TBXA2Rs* and *COX-2* genes in this study. Of the six genes,

the *CysLTR1* -634C > T and 927T > C polymorphisms were significantly associated with LTRA requirement (Table 2), while no significant associations were detected between genetic polymorphisms of the other five genes (*ALOX5*, *ALOX5AP*, *LTC4S*, *TBXA2R* and *COX-2*) and LTRA requirements in AIA patients. The pharmacogenetic effect on LTRA requirement of the *ALOX5* tandem repeat and *LTC4S* polymorphism in our Korean population were not consistent with a Caucasian population. In a recent pharmacogenetic study of LTRA, the genetic variant of *ALOX5* tandem repeat was associated with reduced risk of an exacerbation in receiving montelukast of nonaspirin-sensitive asthmatic patients [27]. However, a lack of association of the *ALOX5* tandem repeat polymorphism with the bronchodilator response to adenosine 5'-monophosphate (AMP) following treatment with LTRA was reported in 52 asthmatics from Scotland [24]. For the *LTC4S* genetic polymorphism, patients carrying the variant genotype showed a more favorable response to LTRA compared with those carrying the common genotype in nonaspirin-sensitive asthmatic patients [20–22,27]. However, a negative association of the *LTC4S* promoter polymorphism with response to LTRA has been also reported [18]. Although the pharmacogenetic effect of *ALOX5* and *LTC4S* polymorphisms on LTRA has remained controversial, these two genes have key roles in leukotriene synthetic pathway and further pharmacogenetic studies will be needed to evaluate the interpatient variability of LTRA responses in AIA patients.

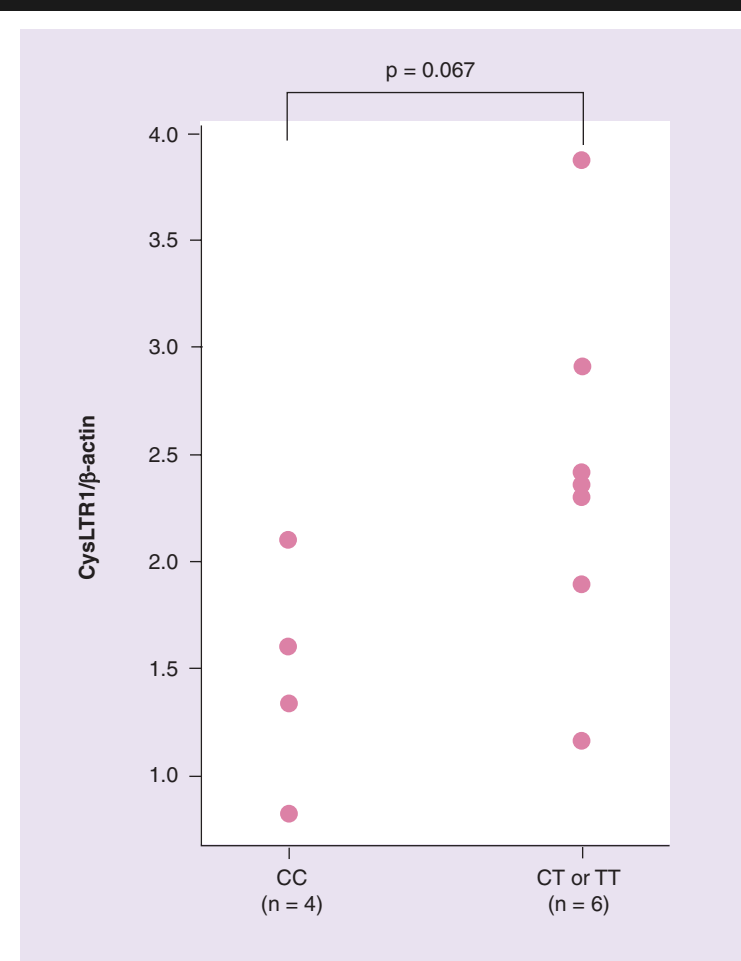
This is the first study to demonstrate a significant association between *CysLTR1* genetic polymorphism and LTRA requirement in AIA patients. Patients carrying variant genotypes of the *CysLTR1* polymorphism consistently required LTRA for the management of AIA. Moreover, patients carrying the variant genotype (CT or TT) of *CysLTR1* -634C > T polymorphism showed a tendency for higher *CysLTR1* mRNA levels relative to those carrying the common genotype (CC), which is consistent with our previous finding that nucleotide substitution of C to T at position -634 from the transcription start site enhanced promoter activity *in vitro* [11]. Moreover, increased surface expression of CYSLTR1 protein using CYLTR1-promoter (T allele)-coding region construct was noted in human airway epithelial cells and mononuclear cells (data not shown). Our recent study demonstrated that

Table 2. Association between arachidonate-related genes and LTRA requirement in 89 patients with AIA.

Gene	SNP	Genotype	Group I	Group II	Group III	p-value	
						I vs II	I vs III
ALOX5	-1708G > A	GG	13/23 (56.5%)	15/21 (71.4%)	14/20 (70.0%)	0.360	0.528
		AG or AA	10/23 (43.5%)	6/21 (28.6%)	6/20 (30.0%)		
	(sp1)n	q	0.217	0.190	0.150	0.797	0.580
		(sp1)5/(sp1)5	13/36 (36.1%)	6/24 (25.0%)	8/27 (29.6%)	0.410	0.788
	(sp1)5/(-) or (-)/(-)	q	0.403	0.479	0.426	0.455	0.856
		23/36 (63.9%)	18/24 (75.0%)	19/27 (70.4%)			
	21C > T	CC	10/20 (50.0%)	10/19 (52.6%)	14/21 (66.7%)	1.000	0.350
		CT or TT	10/20 (50.0%)	9/19 (47.4%)	7/21 (33.3%)		
	270G > A	q	0.250	0.263	0.214	1.000	0.796
		GG	23/23 (100%)	19/21 (90.5%)	19/22 (86.4%)	0.222	0.109
	AG or AA	q	0.000	0.048	0.068	0.225	0.113
		0/23 (0%)	2/21 (9.5%)	3/22 (13.6%)			
ALOX5AP	(A)n	AA	20/22 (90.9%)	19/20 (95.0%)	22/22 (100%)	1.000	0.488
		AG or GG	2/22 (9.1%)	1/20 (5.0%)	0/22 (0.0%)		
		q	0.045	0.025	0.000	1.000	0.494
	218A > G	(A)23/(A)23	24/36 (66.7%)	16/24 (66.7%)	23/27 (85.2%)	1.000	0.144
		(A)23/(-) or (-)/(-)	12/36 (33.3%)	8/24 (33.3%)	4/27 (14.8%)		
		q	0.167	0.188	0.093	0.809	0.296
CysLTR1	-634 C > T	AA	28/28 (100%)	22/22 (100%)	24/24 (100%)	NA	NA
		q	0.000	0.000	0.000	NA	NA
		CT or TT	8/37 (21.6%)	14/25 (56.4%)	14/27 (51.9%)	0.007	0.017
	927T > C	q	0.608	0.340	0.333	0.006	0.002
		TT	11/35 (31.4%)	15/23 (65.2%)	14/24 (58.3%)	0.016	0.060
		CT or CC	24/35 (68.6%)	8/23 (34.8%)	10/24 (41.7%)		
LTC4S	-1072G > A	q	0.500	0.239	0.250	0.006	0.008
		GG	22/33 (66.7%)	17/21 (81.0%)	15/21 (71.4%)	0.354	0.772
		AG or AA	11/33 (33.3%)	4/21 (19.0%)	6/21 (28.6%)		
	-444A > C	q	0.182	0.119	0.143	0.430	0.792
		AA	27/37 (73.0%)	20/24 (83.3%)	17/26 (65.4%)	0.534	0.583
		AC or CC	10/37 (27.0%)	4/24 (16.7%)	9/26 (34.6%)		
TBXA2R	795T > C	q	0.149	0.100	0.173	0.587	0.806
		TT	9/31 (29.0%)	7/23 (30.4%)	7/25 (28.0%)	1.000	1.000
		CT or CC	22/31 (71.0%)	16/23 (69.6%)	18/25 (72.0%)		
	924T > C	q	0.444	0.400	0.420	0.711	0.854
		TT	18/25 (72.0%)	10/20 (50.0%)	13/25 (52.0%)	0.216	0.244
		CT or CC	7/25 (28.0%)	10/20 (50.0%)	12/25 (48.0%)		
COX-2	-162C > G	q	0.140	0.275	0.260	0.122	0.211
		CC	27/27 (100%)	21/21 (100%)	23/23 (100%)	NA	NA
		q	0.000	0.000	0.000	NA	NA
	10T > G	TT	27/27 (100%)	22/22 (100%)	25/25 (100%)	NA	NA
		q	0.000	0.000	0.000	NA	NA
	228G > A	GG	27/27 (100%)	20/20 (100%)	22/22 (100%)	NA	NA
		q	0.000	0.000	0.000	NA	NA

n: Number of patients; q: Minor allele frequency; NA: Not applicable.

Figure 1. mRNA expression level of *CysLTR1* according to the *CysLTR1* -634C>T polymorphism within AIA patients.



Statistical analysis was performed using Mann–Whitney U-test.

when AIA patients present more aggravated asthmatic symptoms after aspirin challenges, the expression level of *CYSLTR1* mRNA from peripheral mononuclear cells increased significantly [28]. Szeffler *et al.* suggested in childhood asthma that the patients with higher urinary LTE4 level showed more favorable response to LTRA [29]. We also found a significant association with *CYSLTR1* 927 T>C, but this is a synonymous SNP, not a change in protein expression. Therefore, we did not apply multiple comparison analysis as the pharmacogenetic effect of *CYSLTR1* found in this study is mainly derived from that of *CYSLTR1* -634 C > T. Taken together, these data suggest that patients carrying the variant genotype (CT or TT) of the *CysLTR1* promoter polymorphism continuously overtranscribe *CysLTR1* mRNA, which exacerbates their asthma symptoms, especially in AIA patients who have a persistently

high production of CysLT. Hence, they may require LTRA longer or permanently to control their asthmatic symptoms.

This study has several limitations. In our study, as most AIA patients had moderate persistent degree of asthmatic symptoms, all subjects regularly used inhaled corticosteroid and so the study evaluated the add-on effect of LTRA. However, in our previous study, when we evaluate the genetic effect of *CysLTR1* at -634 C > T when using inhaled corticosteroid (budesonide 400 ug/day) in 50 asthmatic patients, no associations were found between this *CysLTR1* genotype and all the clinical parameters [Unpublished data], suggesting that *CysLTR1* -634 C > T polymorphism had minimal effect on response to inhaled corticosteroid, but may affect a pharmacogenetic effect of leukotriene modifier. In addition, the numbers of study subjects were limited, so we could not correct for multiple testing.

To the best of our knowledge, our finding is the first to demonstrate a significant association between LTRA requirement and a *CysLTR1* promoter polymorphism in the long-term management of AIA patients. The study was performed in a real-life setting of the chronic management of AIA within a Korean population. The *CysLTR1* gene polymorphism is a useful gene marker for determining AIA susceptibility, as well as an important independent marker for predicting LTRA requirement in the long-term management of AIA patients.

In conclusion, this study demonstrates that the *CysLTR1* promoter polymorphism is a useful genetic marker for predicting LTRA requirements in the long-term management of AIA patients.

Future perspective

LTRA has been widely prescribed as a disease modifier in long-term management of mild-to-moderate asthma, and most clinicians agree that the clinical effect of LTRAs was variable from individual to individual. Moreover, LTRA is the first line drug to be maintained daily to control asthmatic symptoms with inhaled corticosteroid for AIA, there has been no pharmacogenetic data for predicting LTRA response in AIA patients. As we previously reported this *CysLTR1* promoter polymorphism may be involved in AIA pathogenesis, this study demonstrated first that *CysLTR1* polymorphism may have a pharmacogenetic effect of LTRA, which may be applied for predicting LTRA response in the real-life setting of clinical practice. Based on this data, if we further investigate candidate genes in this setting and related

Executive summary

- Leukotriene overproduction is a key finding of aspirin-intolerant asthma (AIA) pathogenesis, and the leukotriene receptor antagonist (LTRA) is known as an effective agent to suppress leukotriene-related airway inflammation and improve asthma control in AIA patients. Therefore, LTRA has been widely used as the first-line treatment to be maintained for effective asthma controls in patients with AIA.
- This study investigated the pharmacogenetic effects of the arachidonate-related genes including *ALOX5*, *ALOX5AP*, *CysLTR1*, *LTC4S*, *TBXA2R* and *COX-2* on the LTRA requirement in the real-life setting of AIA patient with long-term follow-up period, and found that *CysLTR1* -634 C>T polymorphism had a significant pharmacogenetic effect on LTRAs in AIA patients, while no significant associations were found with *LTC4S* and other leukotriene-related genes.
- In this study, we first demonstrated that the *CysLTR1* promoter polymorphism can be an applicable genetic marker for predicting LTRA requirements in the long-term management of AIA patients.

signals under the *CysLTR1* gene, we will be able to find a new insight on the pathogenic mechanism of AIA, and a new therapeutic target for AIA management.

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