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Update on the Management of ASA-intolerant Asthma

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WHAT ARE THE DIFFERENCES IN CLINICAL CHARACTERISTICS BETWEEN ASA-INTOLERANT AND ASA-TOLERANT ASTHMA PATIENTS?

Our previous survey indicated that aspirin (acetyl salicylic acid, ASA) and other non-steroidal anti-inflammatory agents (NSAIDs) were the most common causes of drug allergies, presenting as asthma, urticaria and anaphylaxis.[1] The prevalence of ASA-intolerant asthma (AIA) has been reported as 10～20% in adult asthma.[2,3] AIA's characteristic symptoms include moderate to severe asthma, intense eosinophilic inflammation of upper and lower airway mucosa, and high prevalence of chronic rhinosinusitis and/or nasal polyps.[4,5] In some AIA patients, these symptoms are combined with urticaria or anaphylaxis. Table 1 summarizes the clinical characteristics of AIA and ASA-tolerant asthma (ATA) patients, based on Korean populations.[6] Compared with ATA patients, AIA patients were more commonly found in middle-aged women. The rate of atopy was lower in AIA, but some AIA patients also exhibited allergic asthma. The prevalence of rhinosinusitis and nasal polyps was significantly higher in AIA patients. Baseline forced expiratory volume in 1 s (FEV_1, %) and the degree of airway hyperresponsiveness to methacholine were significantly lower in AIA patients, indicating that AIA patients present with more severe clinical symptoms.

BIOCHEMICAL AND CELLULAR PATHOGENIC MECHANISMS IN AIA

1. Overproduction of cysteinyl leukotrienes and increased expression of Cys-LT receptor 1

Many studies of AIA have focused on the archidonate pathway,[5] owing to the effect of ASA on the cyclo-oxygenase (COX) pathway. NSAIDs, including ASA, inhibit the COX pathway, causing arachidonate metabolites to be diverted to the 5-lipoxygenase (ALOX5, or 5-LO) pathway, where they are then converted to cysteinyl leukotrienes (Cys-LTs) by ALOX5 and its cofactor, 5-lipoxygenase activating protein (ALOX5AP, also known as FLAP). LTC_4 synthase (LTC_4S) is the terminal enzyme in the production of Cys-LTs. The actions of Cys-LTs produce many of the typical features of asthma, including bronchoconstriction, increased vascular permeability, mucus secretion, and eosinophil recruitment, smooth muscle hypertrophy, and fibrous collagen deposition.[7] Cys-LTs are released into nasal and bronchial secretions upon exposure to ASA.[8,9] The level of leukotriene E_4 (LTE_4) in the urine of most AIA patients is 2- to 10-fold that of ATA patients.[10] The airway mucosa is more sensitive to inhaled Cys-LTs in AIA patients compared with ATA patients. Thus, Cys-LTs are regarded as major mediators of AIA pathogenesis.

The biological activities of Cys-LTs are initiated by the binding of Cys-LTs to their receptors, Cys-LT receptors 1 and 2 (CYSLTR1 and CYSLTR2, respectively), which are present on the surface of inflammatory cells.[11,12] The number of cells expressing CYSLTR1 was significantly higher in the nasal mucosa of AIA patients compared with ATA patients, suggesting that the enhanced response of inflammatory cells to Cys-LTs may be related to the over-expression of CYSLTR1.[13,14] Further studies are needed to examine the relationship between CYSLTR1 and CYSLTR2. Thus, the key finding in the pathogenesis of AIA is the over-production of Cys-LTs and the increased expression of CYSLTR1.

2. Dysregulation of cyclo-oxygenase and prostaglandins

The COX enzyme has two isoforms, COX-1 and COX-2, both of which are inhibited by ASA and other NSAIDs. However, NSAIDs are more potent inhibitors of COX-1 than COX-2, and specific COX-2 inhibitors can be tolerated by AIA patients. A previous study demonstrated the down-regulation of COX-2 expres-

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Table 1. Clinical characteristics of Korean AIA patients compared with ATA patients

	AIA (n=163)	ATA (n=197)	*P*-value
Gender (male/total)	62/163 (38.0%)	84/197 (42.6%)	0.390
Atopy (presence/total)	84/151 (55.6%)	132/197 (68.7%)	0.013
Age (years)*	43.3±13.6	40.5±14.1	0.057
Log [serum total IgE (IU/mL)]*	2.2±0.6	2.2±0.7	0.707
Asthma duration (years)*	6.5±5.8	4.0±5.9	0.021
Baseline FEV_1 (%)	79.3±27.2	87.6±22.2	0.002
Fall of FEV_1 by aspirin (%)*	22.8±11.3	7.0±3.9	<0.001
PC_{20} methacholine (mg/mL)*	4.6±7.9	8.8±10.0	<0.001
Paranasal sinusitis (presence/total)	59/128 (46.83%)	9/191 (4.71%)	<0.001
Nasal polyp (presence/total)	67/126 (51.94%)	10/191 (5.24%)	<0.001
Rhinitis (presence/total)	103/129 (80.47%)	140/191 (73.3%)	0.180

*Data are expressed as means±SD. AIA = aspirin-intolerant asthma; ATA = aspirin-tolerant asthma; FEV_1 = forced expiratory volume in 1 s.

sion in nasal polyp tissue from AIA patients, suggesting dysregulation of COX-2 in AIA patients.[15)]

Inhalation of prostaglandin E_2 (PGE_2) inhibited ASA-induced bronchoconstriction and reduced the LTE_4 level in the urine of AIA patients.[16)] Basal PGE_2 production by nasal epithelial cells was lower in AIA patients, and this difference was obvious after exposure to ASA.[17)] Lower production of PGE_2 was also noted in peripheral blood cells[18,19)] and cultured bronchial fibroblasts from ASA-intolerant rhinitis patients.[20)] Moreover, lower PGE_2 production in airway smooth muscle cells was accompanied by simultaneous down-regulation of COX-2 mRNA expression. These findings suggest that ASA/NSAIDs may enhance the depletion of the protective prostaglandin, PGE_2, in association with the down-regulation of COX-2.

3. Activation of the 15-lipoxygenase (15-LO) pathway and production of 15-hydroxyeicosatetraenoic acid and lipoxin

The production of 15-Hydroxyeicosatetraenoic acid (15-HETE) by peripheral blood leukocytes from AIA patients was reported to be 3.6-fold higher than that in ATA patients, and 15-HETE production was enhanced in AIA patients after ASA exposure.[21,22)] However, the mechanism remains unclear. The pro-inflammatory actions of 15-HETE include the stimulation of pro-inflammatory mediators from mast cells, the induction of mucous glycoprotein secretion in human airways, and the contraction of human bronchial smooth muscle. It also exhibits anti-inflammatory activities, including the inhibition of 5-LO activity, the generation of leukotriene B_4 (LTB_4) in leukocytes, and the production of lipoxin, which in turn has several anti-inflammatory actions.[23-25)]

4. Th2 immune response to staphylococcal superantigens and autoimmune responses

AIA patients commonly show chronic rhinosinusitis or nasal polyps. Therefore, we examined the prevalence of specific IgE to three staphylococcal superantigens [staphylococcal enterotoxins A (SEA) and B (SEB), and toxic shock syndrome toxin-1 (TSST-1)] in the sera and nasal polyp tissue homogenates from AIA patients. The AIA patients with high serum specific IgE levels also had more severe airway hyperresponsiveness, and the levels of specific IgE to these superantigens were closely correlated with the eosinophil activation status in nasal polyp tissue. These findings indicate the involvement of a Th2 immune response to staphylococcal superantigens in AIA pathogenesis and nasal inflammation.[26,27)] Other findings have demonstrated the presence of circulating IgG autoantibodies to cytokeratin 18 and 19 in the sera of AIA patients, suggesting the involvement of an autoimmune reaction to autoantigens derived from structural proteins of bronchial epithelial cells.[28)]

5. Mechanism of eosinophil and mast cell activation

Immunohistochemical studies have demonstrated that eosinophil and mast cell counts were significantly higher in AIA than in ATA patients and that LTC_4S and 5-LO expression was higher in eoinophils from AIA patients, indicating that the 5-LO pathway may be involved in the pathogenic mechanism of eosinophilic inflammation in nasal polyp tissue.[29)] Our previous study[30)] on eosinophil activation status demonstrated that the eosinophilic cationic protein (ECP) level was higher in nasal polyp tissue from AIA

patients. Matrix metalloproteinase 9 (MMP9), transforming growth factor-β1 (TGF-β1), and specific IgE to staphylococcal superantigen may be related to eosinophil migration into nasal polyp tissues. Increased expression of eotaxins was noted during eosinophil activation in nasal polyp tissue.[31] Regarding the mast cell activation mechanism, increased tryptase levels were found in nasal lavage fluid after ASA challenge tests, suggesting that ASA may directly activate mast cells.[32] Viral infection was the most important triggering factor for asthma exacerbation in AIA patients.[33,34] Thus, we suggest that triggers such as viruses may activate epithelial cells and T cells, causing them to release cytokines, which recruit eosinophils and mast cells, which is is similar to that of allergic inflammation. However, once initiated, inflammation is further exacerbated in AIA patients because of impaired regulatory mechanisms related to local deficiencies in PGE_2 and lipoxin production, which may lead to upregulation of Cys-LTs and their receptors.

MOLECULAR MECHANISMS SIGNIFICANTLY ASSOCIATED WITH THE AIA PHENOTYPE (Table 2)

1. Human leukocyte antigen allele as a gene marker for AIA phenotype

The association of HLA DPB1*0301 with AIA has been first reported in a Polish population[35] and has since been demonstrated in a Korean population.[36] Patients with DPB1*0301 presented with lower FEV_1 values and with symptoms combined more frequently with rhinosinusitis and/or nasal polyps, which are characteristic clinical features of AIA. Furthermore, AIA patients carrying HLA DPB1*0301 were more dependent on CYSLTR1 antagonists to maintain long-term control of their asthma.[37] Gene interactions between this HLA DPB1*0301 and tumor necrosis factor-α (TNF-α) promoter polymorphisms which is located on the same chromosome 6 have been suggested to occur in AIA patients.[6]

2. The CYSLTR1 gene may be the key to AIA susceptibility

A single nucleotide polymorphism (SNP) identified in the CYSLTR1 gene promoter (−634C>T) was shown to be associated with the AIA phenotype.[38] This polymorphism has also been seen in Japanese asthmatic patients.[39] An *in vitro* functional study demonstrated that the enhanced promoter activity of this mutant genotype could increase the expression of CYSLTR1. An *in vivo* functional study demonstrated that CYSLTR1 mRNA expression was significantly increased after ASA exposure, with exacerbation of symptoms in AIA patients.[40] These results suggest that increased expression of CYSLTR1 could contribute to the development of asthmatic symptoms in AIA patients.

3. Gene polymorphisms in other leukotriene-related genes, including 5-LO and LTC_4S

Two promoter polymorphisms have been identified in the LTC_4S gene (−1072G>A and −444A>C), and −444A>C was shown to be associated with the AIA phenotype in a Polish population.[41,42] The homozygous −444A allele was associated with a greater

Table 2. Summary of genetic studies of AIA in Korean cohorts

Gene	Locus	SNP	Phenotype	Risk	Number	Year
ALOX5	10q11	$(GGGCGG)_{4,6}$	AHR	Higher	107 AIA	2005[47]
FC ε RI β	11q13	−109T>C	IgE to SEB	Lower	164 AIA	2006[58]
TBXA2R	19p13.3	795T>C	FEV_1 fall after L-ASA BPT	Higher	93 AIA	2006[51]
CYSLTR1	Xq24	−634C>T	AIA	Higher	105 AIA	2006[38]
CYSLTR2	13q14.12 −q21.1	2078C>T 2534A>G	FEV_1 fall after L-ASA/oral provocation test	Higher	66 AIA	2005[59]
TGFB1	19q13.2	−509C>T	Rhinosinusitis	Higher	203 AIA	2007
PTGER2	14q22.1	−616C>G, −166G>A	AIA	Higher	108 AIA	2007[49]
PTGER3	1p31.1	−1709T>A	AIA	Higher	108 AIA	2007[49]
PTGER4	5p13.1	−1254A>G	AIA	Higher	108 AIA	2007[49]
PTGIR	19q13.32	1915T>C	AIA	Higher	108 AIA	2007[49]
GPR44	11q12.2	−466T>C	AIA	Higher	108 AIA	
HLA	6	DPB1*0301	AIA	Higher	76 AIA	2004[36]

AIA = aspirin intolerant asthma; SNP = single nucleotide polymorphism; AHR = airway hyperresponsiveness; SEB = staphylococcal endotoxin B; FEV_1 = forced expiratory volume in 1 s; L-ASA = lysine aspirin; BPT = bronchoprovocation test.

increase of urinary LTE_4 after ASA challenge in a Japanese population,[43] and this genetic variation could increase the *in vivo* and *in vitro* transcription rate of LTC_4S. This finding has not been replicated in Korean or other populations.[44,45]

An ALOX5 gene promoter polymorphism, consisting of a variable number of tandem repeats of GC-rich motifs, in association with binding sites for Sp1 transcription factors has been associated with AIA.[46] This polymorphism has been shown to be associated with the severity of airway hyperresponsiveness in a Korean population.[47] Recently, 10 SNPs in leukotriene-related genes (ALOX5: −1708G>A, 21C>T, 270G>A, 1728G>A; ALOX5AP: 218 A>G; COX-2: −162C>G, 10T>G, R228H G>A; LTC4S: −444A>C; and CYSLTR1: 927T>C) were screened in AIA patients in a Korean population. The possible involvement of ALOX5-ht1 (G-C-G-A) with the AIA phenotype was noted, whereas no associations were found with ALOX5AP, COX-2, or CYSLTR1 gene polymorphisms.[44]

4. Dysregulation of the COX pathway, including COX, PEG_2, and the thromboxan A2 receptor (TBXA2R) gene

In a case-control study of 63 candidate prostaglandin-related genes in a Japanese population, a functional SNP in the PGE_2 receptor subtype 2 (EP2) gene was associated with AIA, by reducing the braking effect of PGE_2 on inflammation.[48] Our recent data also demonstrated significant associations of prostanoid receptor genes PTGER2 (−616C>G, −166G>A), PTER3 (−1709T>A), PTGER4 (−1254A>G), and PTGIR (1915T>C) with the AIA phenotype.[49] A study in a Polish population demonstrated significant associations of promoter polymorphisms in the COX-2 gene with gender, atopy, and increased PGE_2 production in AIA patients.[50] A polymorphism in TBXA2R (795T>C), a receptor for a potent bronchoconstrictor, was identified in a Korean population and may increase the bronchoconstrictive response to inhaled ASA, which could contribute to the development of the AIA phenotype.[51]

Table 3. Performance of diagnostics methods used to confirm/exclude ASA-hypersensitivity in patients with AERD

Method	Sensitivity	Specificity
Bronchial	90%	100%
Nasal	73~86.7%	84~95.7%
CAST-ELISA	20~72%	83~100%
BASO test	41.7%	100%
ASPI test	82%	83%

AERD = aspirin-exacerbated respiratory disease; CAST-ELISA = cellular antigen stimulation test-enzyme-linked immunosorbant assay; BASO test = human basophil degranulation test; ASPI test = aspirin-sensitive patient identification test.

DIAGNOSIS AND MANAGEMENT

Diagnosis of aspirin sensitivity among asthmatic patients has been determined by challenge tests. There are four types of challenge tests, which differ in the route of aspirin administration: oral, bronchial, nasal, and, rarely, intravenous. Both oral and bronchial tests have similar specificity, but the oral test has somewhat higher sensitivity. However, oral aspirin challenges can induce severe reactions and take several days to complete. Therefore, the lysine-aspirin bronchial challenge test, which test for a more than 20% decrease in FEV_1 after lysine-ASA inhalation, is widely used in Europe and Asia.[52] As an *in vitro* test, the measurement of 15-HETE released from peripheral blood mononuclear cells stimulated by aspirin exposure has been suggested as an "aspirin-sensitive patient identification" (ASPI) test; however, it is not sufficiently sensitive and is not easy to apply in practice. The sensitivity and specificity of the tests are summarized in Table 3.[53]

When aspirin sensitivity has been confirmed in an asthma patient, complete avoidance of aspirin/NSAID-containing drugs is essential to prevent life-threatening adverse reactions. Table 4[53] summarizes the COX-1 and COX-2 inhibitors that cross-react with ASA. Highly selective COX-2 inhibitors can be prescribed for AIA patients, but, first an oral provocation test is needed to confirm safety.

Table 4. Cross-reactivity of non-steroidal anti-inflammatory drugs in patients with aspirin-exacerbated respiratory disease

High (30~100%) cross-reactivity	Low (5~30%) cross-reactivity
Diclofenac	Paracetamol
Etololac	Diflunisal
Flurbiprofen	Nimesulide
Ibuprofen	Meloxicam
Indomethacin	
Ketoprofen	
Ketorolac	Well tolerated (<1%) cross-reactivity
Mefenamic acid	Celecoxib
Meclofenamate	Rofecoxib
Nabumetone	
Naproxen	
Piroxicam	
Sulindac	

The basic principle of pharmacotherapy for AIA patients is identical to that for ASA-tolerant asthma patients: a step-wise approach, following the 2006 GINA guidelines.[54] Leukotriene receptor antagonists (LTRAs) can be considered as first-line agents to control asthmatic symptoms and are also beneficial in rhinitis and nasal polyps.[55,56] Aspirin desensitization may reduce inflammatory symptoms in the upper and lower airway mucosa[56] and is used in the United States; however, it is not easy to maintain an ASA-desensitized state for many years. Aspirin desensitization is not widely used in Asian countries.

PHARMACOGENETICS FOR AIA PATIENTS

Although several reports have indicated possible associations between genetic polymorphisms and variable responses to leukotriene modifiers in non-aspirin sensitive asthmatic patients,[57] there have only been two published reports suggesting significant associations with LTRAs in Korean populations. The first study suggested that HLA DPB1*0301 may be a useful genetic marker for predicting more favorable responders to LTRAs for long-term management of AIA.[37] The second study[57] investigated possible associations between genetic polymorphisms in 16 leukotriene-related genes, including LTC4S, ALOX5, TBXA2R, COX2, and CYSLTR1, and the responses to LTRAs in long-term management of Korean AIA patients. Patients carrying the T allele of the CYSLTR1 promoter polymorphism (−634C>T) were shown to require significantly higher doses of LTRAs to control asthmatic symptoms, and no significant association was found for the other leukotriene-related gene polymorphisms examined, including ALOX5 and LTC_4S. These results suggest that the CYSLTR1 promoter polymorphism at −634C>T may be a useful genetic marker for predicting more favorable responders to LTRAs in the long-term management of chronic AIA. Taken together, the HLA DPB1*0301 allele and the CYSLTR1 promoter polymorphism (−634C>T) may be useful genetic markers for predicting AIA susceptibility and the long-term requirement for LTRAs in AIA patients. Furthermore, ALOX5, LTC4S, $PTGER_2$, TBXA2R, and CYSLTR1 may be viable targets for future pharmacogenetic studies in AIA patients. The pharmacogenetic effects of other asthma drugs, including long- acting beta-2 agonists and corticosteroids, should be evaluated in larger cohorts of AIA patients. Additional molecular genetic studies, including whole-genome association studies, to identify susceptible genetic markers for AIA may provide molecular markers for predicting drug response variability in AIA patients.

CONCLUSIONS

Additional pathogenic studies, including autoimmune and whole-genome studies, along with supporting functional studies will help to further elucidate the pathogenic mechanism of AIA. This may lead to the development of new diagnostic markers and therapeutic targets for AIA patients.

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