Review Article | DOI 10.3349/ymj.2009.50.6.744 pISSN: 0513-5796, eISSN: 1976-2437 | Yonsei Med J 50(6): 744-750, 2009 | YMJ

Update on Recent Advances in the Management of Aspirin Exacerbated Respiratory Disease

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Aspirin intolerant asthma (AIA) is frequently characterized as an aspirin (ASA)-exacerbated respiratory disease (AERD). It is a clinical syndrome associated with chronic severe inflammation in the upper and lower airways resulting in chronic rhinitis, sinusitis, recurrent polyposis, and asthma. AERD generally develops secondary to abnormalities in inflammatory mediators and arachidonic acid biosynthesis expression. Upper and lower airway eosinophil infiltration is a key feature of AERD; however, the exact mechanisms of such chronic eosinophilic inflammation are not fully understood. Cysteinyl leukotriene over-production may be a key factor in the induction of eosinophilic activation. Genetic studies have suggested a role for variability of genes in disease susceptibility and response to medication. Potential genetic biomarkers contributing to the AERD phenotype include HLA-DPB1*301, LTC4S, ALOX5, CYSLT, PGE2, TBXA2R, TBX21, MS4A2, IL10 -1082A > G, ACE -262A > T, and CRTH2 -466T > C; the four-locus SNP set was composed of B2ADR 46A > G, CCR3 -520T > G, CysLTR1 -634C > T, and FCER1B -109T > C. Management of AERD is an important issue. Aspirin ingestion may result in significant morbidity and mortality, and patients must be advised regarding aspirin risk. Leukotriene receptor antagonists (LTRA) that inhibit leukotriene pathways have an established role in long-term AERD management and rhinosinusitis. Aspirin desensitization may be required for the relief of upper and lower airway symptoms in AERD patients. Future research should focus on identification of biomarkers for a comprehensive diagnostic approach.

Key Words: Aspirin, asthma, genetic polymorphism, leukotriene, eosinophil

Received: October 16, 2009
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· The authors have no financial conflicts of interest.

INTRODUCTION

Aspirin is an extremely common drug used for management of pain and inflammation. Aspirin intolerance, asthma, and nasal polyps were described for the first time by Widal and colleagues.[1] Aspirin-intolerant asthma (AIA), also known as acetyl salicylic acid (ASA)-exacerbated respiratory disease (AERD), is a clinical syndrome associated with severe and chronic inflammation in both upper and lower airways resulting in chronic rhinitis, sinusitis, recurrent polyposis, and asthma.[2] AERD presents more severe clinical symptoms and is frequently associated with chronic eosinophilic rhinosinusitis and nasal polyposis, and occasionally with urticaria or anaphylaxis.[2] The prevalence of aspirin hypersensitivity in the general population ranges from 0.6 to 2.5%, and is increased in asthmatics.[3,4] AERD pathophysiology is characterized by abnormalities in the biosynthesis of eicosanoid mediators and eicosanoid receptor expression. Increased cysteinyl leukotrienes (LTC4, LTD4, LTE4) are potent pro-inflammatory mediators and bronchoconstrictors in AERD pathogenesis. Therefore, AERD patients may present more severe asthma phenotypes with irreversible airflow obstruction and frequent exacerbation of symptoms compared to patients with aspirin-tolerant

asthma (ATA).[5]

THE CLINICAL CHARACTERISTICS OF AERD PATIENTS

AERD is characterized by persistent and severe inflammation of the upper and lower respiratory tracts. Therefore, the patients present with chronic eosinophilic rhinosinusitis, nasal polyposis, as well as chronic persistent asthma. The severity of asthma symptoms is usually moderate to severe in nature, and AERD is more common in women. The skin prick test demonstrated that a non-atopic status was more prevalent than an atopic status in a Korean cohort of AERD patients.[6] AERD usually begins during adulthood and is manifested by persistent rhinitis with or without nasal polyps.[7]

THE DIAGNOSIS OF AERD

Some patients have a definitive history of adverse reactions to ASA and NSAIDs; however, 50% of patients in our Korean population had not experienced adverse reactions, suggesting that ASA challenge tests are critical for diagnosis. Most patients demonstrated positive responses to methacholine bronchial challenge tests. The confirmative diagnosis for AERD can be definitively established by aspirin challenges; patients receive increasing doses of oral, inhaled, or nasal lysine aspirin during aspirin challenges. The lysine ASA bronchoprovocation test has been widely used in Korea and Europe. It give rapid results and a similar sensitivity to other tests.[8] Flow-cytometric determination of aspirin-induced basophil activation and aspirin-triggered 15-HETE generation in peripheral blood leukocytes (PBLs) may be highly specific and sensitive diagnostic tools;[9] however, sufficient validation is still required. In addition, further *in vitro* tests including blood eosinophil levels, eosinophilic cationic protein testing, and sputum and nasal eosinophil counts can be measured, and are increased with symptom aggravation in AERD patients.[10]

THE PATHOGENESIS OF AERD

AERD generally occurs due to abnormalities in mediators and expression of arachidonic acid biosynthesis. Elevation of Cys-LT levels in the urine, sputum, peripheral blood, and exhaled breath were previously observed after aspirin challenges in AERD patients.[11] AERD patients had higher exhaled nitric oxide levels and higher baseline levels of CysLTs in saliva, sputum, blood *ex vivo* and urine than subjects with AERD.[10] Leukotriene E4 has elevated potency relative to other CysLTs, and contributes to the increase of histamine-induced airway responsiveness and the enhancement of eosinophic recruitment and resultant increases in vascular permeability, in both the lipooxygenase (LOX) and cyclooxygenase (COX) pathways (Fig. 1).[12]

Arachidonic acid may be metabolized through COX to yield the prostanoids and 5-lipoxygenase (5-LO) pathway and formation of the LTA4, LTB4 and LTC4 metabolites upon phospholipase A2-mediated release from the cell membrane. Hydroperoxidation of arachidonic acid is catalyzed by 15-lipoxygenase (15-LO) to form 15-HPETE; the other products include lipoxins (LXs) and eoxins (EXs). Aspirin-induced inhibition of the COX pathway leads to asthmatic attacks, shunting towards the LOX pathway, enhanced Cys-LT production, and abnormal regulation of the LOX pathway. This has been described in AERD as well. Decreased lipoxin production in AERD compared to ATA has been correlated with increased Cys-LT. AERD may diminish LX biosynthesis capacities *in vivo* after ASA challenge.[13] Cys-LTs exert effects by binding to the Cys-LT receptors Cys-LTR1 and Cys-LTR2.[14,15] A third receptor, GPR17, has been also identified for Cys-LTs.[16] CysLTR1 mediates airway smooth muscle contraction, mucous hypersecretion, and microvascular leakage; CysLTR2 mediates inflammatory responses, potentially through the modulation of chemokine gene transcription and contributes to vascular permeability and tissue fibrosis.[17] Increased Cys-LTR1 expression was detected in the nasal mucosa of patients with AERD compared to ATA patients.[18] Leukotriene receptor antagonists blocked Cys-LTR1, but did not Cys-LTR2.

Aspirin inhibits COX-1 more frequently than COX-2,

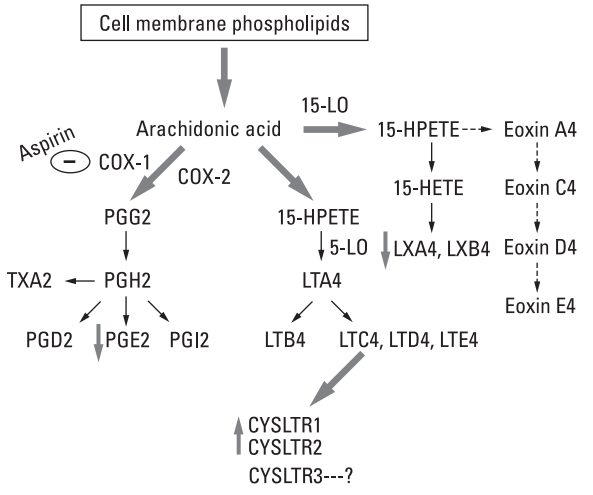

Fig. 1. Schematic representation of the metabolism of arachidonic acid by the cyclooxygenase and the 5-and 15-LO pathways.

and COX-2 inhibitors are usually tolerated by AERD patients.[19] COX-2 expression was downregulated in nasal polyps from AERD patients.[20] COX-2 was differentially regulated in AERD patients in a recent study, and ASA and LPS increased COX-2 expression on blood monocytes compared to healthy subjects.[21] PGE2 is an inhibitor of inflammatory mediator released from mast cells, eosinophils, and macrophages,[22] and decreased PGE2 synthesis by nasal epithelial cells has been reported in AERD patients[23] and may be a primary cause for AERD aggravation despite the lack of clear mechanisms. Reduced PGE2 production in airway smooth muscle cells has also been correlated with down-regulation of COX-2 mRNA expression.[24] This suggested that PGE2 down-regulation could be involved in AERD pathogenesis.

Upper and lower airway eosinophil infiltration is a key feature of AERD. Although the exact mechanisms are unclear, cysteinyl LT over-production may induce eosinophilic activation.[7,25] A previous study demonstrated that serum eotaxin-2 levels were higher in the sera of AERD patients.[26] IL-5 was increased in the nasal mucosa of AERD patients.[27] Eoxin (EX) from the 15-LO pathway may be a possible mechanism of eosinophil activation in AERD patients since severe asthma and aspirin-intolerant asthma markedly enhanced the 15-LO pathway (15-HETE).[28,29] In addition, nasal polyps from allergic subjects spontaneously released EXC_4 in another study.[29] Multiple polyp cell types, including eosinophils, may serve as the EXC_4 source. In addition, *Staphylococcus aureus* enterotoxin (SEB) may down regulate PGE2 receptors, requiring examination of the role SEB and other superantigens in AERD pathogenesis. A previous study showed that SEA/SEB specific IgE was significantly higher in AERD patient sera than in ATA patient sera, and that patients with high serum specific IgE to SEA had lowered PC20 methacholine, suggesting more severe airway hyperresponsiveness.[30] Specific IgE to staphylococcal superantigens were found in nasal polyp tissue homogenate which closely correlated with eosinophil activation status,[31] suggesting that these specific IgE response to superantigens may be involved in upper and lower airway eosinophilic inflammation of AERD patients.

Szczeklik hypothesized that ASA intolerant asthma develops as the result of chronic viral infection.[32] Immunological responses to infection, expressed by specific cytotoxic lymphocytes, is under the inhibitory control of PGE2. Cytotoxic reactions will be preceded if PGE2 removal occurs by COX inhibitor- and cytotoxic lymphocyte-mediated attack and destruction of virus-affected cells of the respiratory tract. Active oxygen species, toxic metabolites, and mediators released in the course of such reactions may precipate asthma. Further, ASA sensitivity is diminished in some AERD patients during acyclovir treatment of herpex simplex infection.[33] IgG4 elevation might result from chronic antigenic stimulation of viral origin in AERD.[34]

GENETIC BIOMARKERS OF AERD

Several recent investigations have suggested that several genetic markers may be used as AERD biomarkers (Fig. 2).

The HLA allele DPB1*0301 may represent the AERD phenotype, and that patients with this allele displayed typical clinical characteristics of Samter's triad with lowered FEV1 levels and increased prevalence of rhinosinusitis with nasal polyps. Further, higher doses of requirements of leukotriene receptor antagonists was required to control asthma symptoms, suggesting that this could serve as a strong biomarker for an AERD phenotype.[35]

Studies have suggested that increased Cys-LT levels are potential AERD markers. An association study demonstrated that the C allele in the LTC4 -444A > C promoter polymorphism was a risk factor for AERD in a Polish population.[36] This was not replications in other populations, including Korean populations.[37,38]

ALOX 5 is another AERD candidate, and ALOX gene promoter polymorphism involved SP1 transcription factor

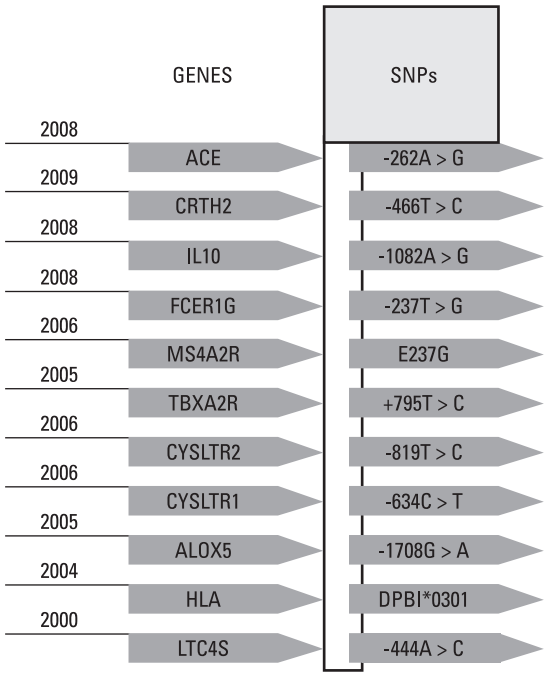

Fig. 2. Genetic markers of AERD. HLA, human leukocyte antigen; LTC4S, leukotriene C4 synthase; ALOX5, arachidonate 5-lipoxygenase; CYSLTR 1, cysteinyl leukotriene receptor 1; CYSLTR2, cysteinyl leukotriene receptor 2; TBXA2R, thromboxane A2 receptor; MS4A2, high affinity immunoglobulin epsilon receptor beta-subunit; FCER1AG,high affinity immunoglobulin epsilon receptor gamma-subunit; IL10, interleukin10; ACE, angiotensin converting enzyme-I.

in previous study.[39] The same polymorphism was associated with the degree of airway hyperresponsiveness in a Korean population.[40] No associations were noted between ALOX5-activating protein (ALOXAP 218A > G), COX 2 (COX-2 -162C > G, 10T > C and 228G > A) and Cys-LTR1 (CYS-LTR1 927T > C) the exon site with AERD in a Korean population, while one ALOX5 ht1 haplotype (G-C-G-A) was associated with AERD development.[9]

Significant associations between three Cys-LTR1 SNPs (-634C > T, -475A > C and -336A > G) and AERD were already reported. Further, an *in vitro* functional study in Jurkat T and A549 cells demonstrated increased promoter activity in the ht2 (T-C-G) construct compared to the ht1 (C-A-A) construct, suggesting that these polymorphisms may be important for AERD. In addition, Cys-LTR1 mRNA expression was significantly increased *in vivo* in peripheral mononuclear cells when AERD patients were exposed to aspirin.[41,42] The frequencies of several rare CYS-LTR2 alleles (-819T > G, 2078C > T and 2534A > G) were also higher in AERD patients than in ATA patients.[43] These SNPs resulted in greater reduction in FEV1 following aspirin provocation.

SNPs (n = 6) were studied in the three genes encoding FCER1 (FCER1A, MS4A2, FCER1G). Significant differences in the genotype frequencies of FCER1G -237A > G were detected between AERD and ATA patients. AERD patients carrying the homozygous AA genotype of FCER1G -237A > G showed significantly higher total serum IgE levels than those with the GG/AG genotype. AERD patients carrying the CT/TT genotype at FCER1A -344C > T showed a higher prevalence of SEA-specific serum IgE than those with the CC genotype. The genotype frequencies of FcepsilonR1beta-109T > C and E237G polymorphisms were not significantly associated with AERD pathogenesis.[44]

A significant association was noted with IL10 -1082A/G and the AERD phenotype. Further, a synergistic effect between the TGF-β1 509C/T and IL-10 1082A/G polymorphisms on the AERD phenotype was noted, and when stratified by the presence of rhinosinusitis was further confirmed with *in vitro* functional assay. The IL10-1082G reporter plasmid exhibited significantly greater promoter activity when compared with the 1082A construct in Jurkat T cells. Identification of the transcription factor Myc-associated zinc-finger protein bound the 1082G allele was reported.[45]

Other markers including TBXA2R and TBX21 have been also reported. TBXA2R +795T > C was associated with AERD susceptibility in a Korean population.[46] Further, the -19993T > C SNP in the TBX21 promoter region was associated with AERD in a Japanese population.[47] These findings were not replicated in a Korean population.[48]

Another recently published study demonstrated an association of angiotensin I-converting enzyme (ACE) gene polymorphisms with aspirin intolerance in asthmatics. The -262 A > T polymorphism in the ACE gene promoter is associated with AERD, and the rare -262 A > T allele may confer aspirin hypersensitivity via the down-regulation of ACE expression.[49]

Serum eotaxin 2 levels were related with the CRTH2 polymorphism in AERD patients. The *CRTH2* -466T > C polymorphism could increase serum and cellular eotaxin-2 production through lowered CRTH2 expression, leading to eosinophilic infiltration in AERD patients.[26]

Gene-gene interactions have been also proposed in AERD pathogenesis, and another study demonstrated that the genetic effects of Cys-LTR2 and LTC4S -444A > C synthesis increased FEV1 lower levels after lysine -ASA inhalation.[43] TBXA2R 795T > C was associated with HLA DPB1*0301 in AERD patients compared with ATA.[46] Significant epistatic effects with a four-locus genetic interaction were reported in AERD susceptibility, including adrenergic, beta-2-receptor, B2ADR, 46A > G, chemokine (C-C motif) receptor 3, CCR3 -520T > C, CysLTR1 -634C > T, and FCER1B -109T > C.[50] Gene interaction with one another resulting in AERD is still unclear.

The proper diagnosis of AERD is a challenge despite the availability of diagnostic techniques. Genetic studies have indicated a role for gene variability in disease susceptibility and medication response. Potential AERD genetic biomarkers include HLA-DPB1*301, leukotriene C4 synthase (LTC4S), ALOX5, CYSLT, PGE2, TBXA2R, TBX21, MS4A2, IL10 -1082A > G, ACE -262A > T, CRTH2 -466T > C together with the four-locus SNP set B2ADR 46A > G, CCR3 -520T > G, CysLTR1 -634C > T and FCER1B -109T > C. Further studies evaluated these genes should include microarray studies as well as integrative genomic, comparative genomic and genome-wide association approaches.

AERD MANAGEMENT

Aspirin ingestion may cause significant morbidity and even mortality, and patients must be counseled accordingly. Most patients can tolerate highly selective COX-2 inhibitors.[19] Acetaminophen poorly inhibits COX-1 and COX-2, and results in rare intolerance with high-dose exposures. A pharmacological approach based on asthma control status should be applied.[51] Combination therapy including inhaled corticosteroid (ICS) and long acting beta2 agonists (LABA) may be applied with leukotriene modifier, particularly with patients at step III or higher levels. The ICSs inhibit eosinophils, macrophages, T-

lymphocytes, mast cells, and other inflammatory markers. LABAs may possess anti-inflammatory properties and may inhibit inflammatory mediator release from mast cells, block plasma exudates, reduce airway edema, and modulate airway sensory nerves that mediate airway hyper-responsiveness.

LEUKOTRIENE RECEPTOR ANTAGONISTS (LTRA)

LTRAs interrupt the leukotriene pathway and have an established role in asthma and allergic rhinitis therapy. Two classes of leukotriene modifier drugs have been approved for asthma treatment: the cysteinyl leukotriene 1 receptor antagonist (montelukast, zafirlukast, pranlukast) and the 5-lipoxygenase (5-LO) inhibitor. Both have been widely prescribed for symptom control in both upper and lower airway of AERD patients.[52,53] Several pharmacogenetic LTRA studies have been reported which consider the genetic polymorphisms of CYSLTR1.[53] Our previous data have suggested that patients carrying the T allele at CYSLTR1 at -634 C > T required higher doses of cysLTR1 antagonists to control their asthmatic symptoms.[42]

MANAGEMENT OF CHRONIC RHINOSINUSITIS AND NASAL POLYPOSIS

Improvement of aspirin intolerance is essential for successful management of chronic rhinosinusitis. Nasal decongestants and antihistamines are used but provide transient relief. Topical corticosteroids are effective in most AERD patients with rhinosinusitis.[54] Several reports have suggested that LTRA could improve rhinosinusitis and nasal polyps without surgery,[55,56] suggesting that endoscopic nasal surgery should be selected for severe chronic sinusitis with multiple nasal polyps and nasal passage obstruction.

ASPIRIN DESENSITIZATION

Aspirin desensitization can be beneficial for some AERD patients with upper and lower airway inflammation; however, it is recommended for AERD patients with corticosteroid-dependent asthma or those requiring daily ASA/NSAID therapy for other medical diseases including coronary artery disease or chronic arthritis. Oral administration with an initial desensitization with incremental doses of aspirin followed by daily high dose therapy may be safe and clinically effective, and may produced definite improvements in both upper and lower respiratory tract symptoms in the majority of patients with aspirin sensitivity.[57] The regimen contains escalating doses of oral aspirin over two to five days until 650 mg can be tolerated twice daily. Aspirin can be reduced after symptom improvement. The precise mechanism by desensitization in aspirin intolerance therapy is unclear. However, leukotriene B4 and thromboxane B4 were reduced in a cell culture model and were similar to normal controls after aspirin desensitization.[58] Another study demonstrated decreased bronchial responsiveness to inhaled leukotriene E4 on the first day of sensitization therapy.[59] Direct modulation of intracellular biochemical pathways of inflammatory cells could serve as another possible mechanism.

CONCLUSIONS

Future areas of investigation should focus on identification of biomarkers for early diagnosis with various diagnostic techniques. AERD has heterogenous phenotypes, and this impairs current diagnostic techniques and there are no current animal models. Increased comprehensions of the molecular, cellular, and biochemical basis of AERD will be helpful for the determination of new diagnostic tools and therapeutic interventions.

ACKNOWLEDGEMENTS

This study was supported by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korean Government (MEST), 2009-0078646.

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