



An update on the management of aspirin-exacerbated respiratory disease

Ji-Ho Lee, Chang-Gyu Jung & Hae-Sim Park

To cite this article: Ji-Ho Lee, Chang-Gyu Jung & Hae-Sim Park (2017): An update on the management of aspirin-exacerbated respiratory disease, Expert Review of Respiratory Medicine, DOI: [10.1080/17476348.2018.1417843](https://doi.org/10.1080/17476348.2018.1417843)

To link to this article: <https://doi.org/10.1080/17476348.2018.1417843>



Published online: 18 Dec 2017.



[Submit your article to this journal](#) 



[View related articles](#) 



[View Crossmark data](#) 

REVIEW



An update on the management of aspirin-exacerbated respiratory disease

Ji-Ho Lee^a, Chang-Gyu Jung^b and Hae-Sim Park^a

^aDepartment of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, South Korea; ^bDivision of Allergy and Clinical Immunology, Department of Internal Medicine, Keimyung University, Dongsan Medical Center, Daegu, South Korea

ABSTRACT

Introduction: Clinical features of aspirin-exacerbated respiratory disease (AERD) consist of moderate to severe asthma associated with chronic rhinosinusitis (CRS), which are derived from overproduction of cysteinyl leukotrienes along with chronic type 2 mediated inflammation in the upper and lower airway mucosa.

Area covered: This review provides recent up-to-date information regarding phenotypes of AERD and encompasses comprehensive diagnostic methods and treatment options. To confirm the diagnosis of AERD, provocation testing via nasal, inhalation or the oral route of aspirin remains the gold standard; *in vitro* diagnostic methods are still not available. Essential management is to avoid cross-reacting cyclooxygenase 1 (COX-1) inhibitors along with use of highly selective COX-2 inhibitors and to maintain pharmacologic treatment depending on the severity of asthma and chronic rhinosinusitis. Recent biologics, including anti-IgE and anti-IL5 antibodies, are required in severe AERD patients with CRS. Aspirin desensitization can be recommended when indicated.

Expert commentary: AERD is a heterogeneous disease in terms of severity and associated allergic disease. When performing diagnosis and treatment for AERD, such disease characteristics need to be kept in mind.

ARTICLE HISTORY

Received 19 October 2017

Accepted 12 December 2017

KEYWORDS

Aspirin-exacerbated respiratory disease; leukotriene; management; provocation test; severe asthma

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) can induce various clinical manifestations of hypersensitivity reactions, which can be classified into cross-reactive and non-cross-reactive reactions. In cross-reactive reactions, aspirin or other NSAIDs elicit hypersensitivity: (1) aspirin-exacerbated respiratory disease (AERD), (2) NSAID-exacerbated cutaneous disease, and (3) NSAID-induced urticaria/angioedema. In non-cross-reactive reactions, single NSAID or several NSAID within a same chemical group elicit hypersensitivity: (4) single-NSAID-induced urticaria/angioedema or anaphylaxis, and single-NSAID-induced delayed hypersensitivity reactions [1]. AERD is clinically diagnosed as developing asthma exacerbation after taking of NSAIDs. However, clinical severity of asthma is moderate to severe, even in the case of not taking of NSAIDs.

AERD is characterized by a distinctive pathogenic mechanism, dysregulated arachidonic acid metabolisms resulting in activation of eosinophilic inflammation [2]. Recently, apart from analysis of asthma phenotype, AERD has been found to consist of different phenotypes and severities [3]. The efficacy of biologic agents targeting IgE is effective for the treatment of AERD [4]. In addition, biologics targeting IL5 can be a promising treatment option. The current review will discuss pathogenesis, clinical features, diagnostic methods, and treatment of AERD with updated information.

2. Clinical features

The prevalence of AERD is reported to range from 7% to 20% of adult asthmatic patients [1,5], which is more prevalent in severe asthmatic patients. AERD most frequently occurs in middle-aged adults, with predominance in females. Chronic rhinosinusitis (CRS) and nasal polyps are the most common comorbid conditions, which affect asthma severity. Both asthma and CRS symptoms can be exacerbated seriously after NSAIDs/aspirin exposure in a dose-dependent manner. The prevalence of AERD in children is lower, but clinical phenotypes are similar [6].

Both atopics and nonatopics are affected with AERD [1,2]. Some AERD patients have high serum total IgE (above the upper limit of normal) without atopy, which may be associated with IgE responses to staphylococcal superantigens [7,8]. AERD patients show more frequent asthma exacerbation (higher prevalence of severe asthma), lung function decline (lower FEV1% values), and need for higher doses of inhaled and systemic steroids to control symptoms [2]. Patients with CRS/nasal polyps suffer from severe persistent nasal obstruction, postnasal drip, and anosmia requiring intranasal steroids. Nasal polyps found in AERD patients undergo rapid regrowth after polypectomies, resulting in frequent sinus surgeries [2,9].

Clinical features and courses of AERD patients are variable. Drug responses to leukotriene modifiers are inconsistent. A recent study reported 4 classes in a Polish cohort of 231 AERD patients: class 1, asthma with a moderate course, intensive

upper airway symptoms, and blood eosinophilia; class 2, asthma with a mild course, with low health-care use; class 3, asthma with a severe course with severe exacerbations and airway obstruction; and class 4, poorly controlled asthma with frequent exacerbations in female subjects. Atopic status did not affect AERD. Patients with intensive upper airway symptoms had the highest levels of blood eosinophils and urinary leukotriene E4 (LTE4) [3].

3. Pathogenesis

Major pathogenetic mechanisms are dysregulation of arachidonic acid metabolisms, especially cysteinyl leukotriene (CysLT) overproduction, and eosinophil activation. NSAIDs/aspirin ingestion in sensitive patients inhibits the cyclooxygenase 1 (COX-1) pathway and reduces prostaglandin E2 (PGE2) levels, which leads to overproduction of CysLTs with increased expression of CysLT receptors [2,10]. Activation status of eosinophils (interacting with activated platelets) with increased level of eosinophil-derived cytokines and chemical mediators, as well as mast cells (increased production of PGD2), is noted along with type 2-mediated inflammation in upper and lower airway mucosa of AERD patients [11]. Recent studies suggested potential mechanisms of eosinophil activation in AERD patients: increased level of autophagy and etosis of eosinophils. Autophagy is a cytoplasmic component within double membrane structures which is delivered to lysosome for degradation [12]. Etosis is a non-apoptotic cell death pathway, extracellular trap cell death (etosis) that mediates the eosinophil cytolytic granule [13]. Both of them are correlated with asthma severity [14] and innate immune responses, such as IL-33 and TSLP, released from airway epithelial cells [15,16]. Further investigations will be needed to identify new therapeutic targets in these pathways. In addition, recent data demonstrate increased activation of the 15-lipoxygenase (LO) pathway and decreased synthesis of lipoxin A4, which are associated with eosinophil activation and clinical outcome [2,10,17].

Genetic and epigenetic factors could influence these findings. Many studies have been devoted to investigating the genetic mechanisms of AERD in AERD cohorts based on diverse ethnic groups. First, the human leukocyte antigen (HLA) allele DPB1*0301 is a strong genetic marker for AERD in Western and Asian populations [17,18], in which the prevalence of this allele was significantly higher in the AERD group than in the control groups. Patients with this allele showed typical clinical characteristics of AERD, including lower FEV1% predicted values and a very high prevalence of CRS with nasal polyps. Several candidate gene approaches are focused on identifying genes related with CysLT synthesis, including the 5-LO pathway and CysLT receptors, and eosinophil activation: the genetic polymorphisms of CysLTR1 (−634 C>T, −475 A>C, −336 A>G), CysLTR2 (−189 T>C), P2RY12 (the third receptor of CysLT at 742 T>C and 18 C>T) have been associated with CysLT overproduction and eosinophil activation [17,19,20]. The genetic polymorphisms of CCR3 (−520 T>C) and CRTH2 (−466 T>C) are associated with eosinophil migration and activation in AERD patients. Another genetic

approach, a genome-wide association study (GWAS) study, demonstrated dipeptidyl-peptidase 10 (DPP10) as a significant gene marker in association with the phenotype of AERD and eosinophil activation [21]. Epigenetic study also provide additional genetic background which account for AERD pathogenesis [22]. Nasal polyps of five AERD patients were investigated using genome-wide methylation assay, along with them of four aspirin-tolerant asthma (ATA) patients [23]. It was found that *PGDS*, *ALOX5AP*, and *LTB4R* were hypomethylated and *PTGES* was hypermethylated, all of which are genes in the arachidonic pathway. PGD synthase encoded from *PGDS* increase production of PGD2. *ALOX5AP* encodes arachidonate 5-LO-activating protein and *LTB4R* encodes leukotriene B4 receptors, whereas *PTGES* encodes PGE synthase, which is attenuated by hypermethylation. Histone acetylation serves to increase exposure of promoter region to transcription factor in chromatin. In a study with experiments using fibroblasts from nasal polyps of AERD patients, impaired histone acetylation at the *PTGER2* promoter could be implicated in decreased expression of PGE2 receptors and resultant rapid growth of nasal polyps in AERD [24]. Regarding environmental factors, viral infections (especially rhinovirus) and staphylococcal superantigens could augment Th2-derived immune responses in the upper and lower airway mucosa of AERD patients [25]. Further studies will be needed to elucidate how genetic/epigenetic mechanisms can be interacted with various environmental factors to present these phenotypes and endotypes.

Therefore, AERD is usually accompanied by blood, nasal, and sputum eosinophilia along with extensive eosinophilic inflammation in upper (including nasal polyps and sinus mucosa) and lower airway mucosae along with increased expression of type 2 cytokines, including IL5 [2]. In addition, levels of activated platelets and platelet-leukocyte aggregates are increased in both the peripheral blood and nasal polyp tissue of AERD patients, which are associated with eosinophil activation and CysLT production [26]. Therefore, the pathogenesis of AERD involves two separate, albeit probably closely related, mechanisms. One is the mechanism underlying NSAIDs/aspirin-induced acute respiratory reactions, which are the hallmark of this syndrome; the other is the mechanism for the development of chronic intractable inflammation of the lower and upper airway mucosa, which is present, even in the absence of exposure to NSAIDs, and underlies the chronicity of the disease.

4. In vivo and in vitro diagnostic methods

The clinical suspicion of AERD is based on a history of adverse reactions precipitated by NSAIDs/aspirin. However, 18% of patients with AERD did not recognize hypersensitivity reactions before aspirin provocation test in a survey [27]. In addition, only one of three subjects regarded as AERD showed positive response to provocation test [28]. Therefore, in patients without a definite history, challenge tests are necessary to confirm or exclude hypersensitivity. The recent the European Academy of Allergy and Clinical Immunology (EAACI) position papers reported guidelines for standardized oral, inhalation, and nasal challenges for patients with NSAID hypersensitivity [1,2,29].

Since most AERD patients have moderate-to-severe asthma, diagnostic methods for adult asthma, such as sputum and blood eosinophil counts, airway reversibility testing with spirometry, and methacholine bronchial challenge tests, should be performed to evaluate the degree of asthma severity. As AERD patients present with more severe clinical symptoms, they show lower mean values of PC20 methacholine (more severe airway hyperresponsiveness to methacholine) and FEV1(%) [2]. Allergy skin tests and determination of serum-specific IgE to common inhalant allergens are needed to evaluate atopic status as well as associated allergic rhinitis and asthma. To confirm the diagnosis of AERD, three types of aspirin-provocation tests are widely applied: oral, inhalation (bronchial), and nasal [1,2,29], which should be carried out in a clinical setting under the direct supervision of an experienced specialist. Emergency resuscitative equipment should be readily available. Baseline FEV1 should be at least 70% of the predicted value. All the challenge tests are preceded by placebo challenge. Before any challenges, withdrawal of several types of antiasthmatic medications is indicated: short-acting β_2 -agonists and ipratropium bromide, 6 h; long-acting β_2 -agonists, long-acting theophylline, and tiotropium bromide, 24 h (48 h if possible); short-acting oral antihistamines, 3 days; and leukotriene modifiers, at least 1 week. However, there are evidences to support continuing treatment with leukotriene receptor antagonists (LTRAs) as a premedication. LTRAs do not prevent upper respiratory reactions, whereas they prevent or attenuate significant aspirin-induced bronchospasm during oral challenge [30,31]. Oral and inhalation challenges should not be performed on patients with unstable asthma or FEV1 lower than 70% of the predicted value or less than 1.5 L. If regular treatment with oral corticosteroids is required, the doses should not exceed 10 mg prednisolone or equivalent. The doses of bronchial and nasal corticosteroids should be as low as possible and kept stable throughout the challenge. The lysine-aspirin bronchoprovocation test is widely used in Asia [2] and Europe [1], and its detailed standardized test protocol has been published. This inhalation challenge is safer and faster to carry out than the oral provocation test, although it is less sensitive. Inhalation challenge involves administration of increasing doses of lysine-aspirin using a dosimeter-controlled nebulizer every 30 min, with FEV1 measurement every 10 min after each administration. Criteria for a positive response are the same as for oral aspirin challenge (greater than 20% fall in FEV1% predicted from the baseline value). In

cases of a positive reaction, symptoms are relieved by inhalation of a short-acting β_2 -agonist until FEV1 returns to the baseline value. If more severe reactions occur, oral or intravenous corticosteroids are administered. A negative result of an inhalation test does not always exclude AERD; subsequently, an oral aspirin challenge can be also performed if necessary.

Controlled oral challenge with aspirin is regarded as the gold standard which is recently standardized [1,29,32]. This challenge is the most sensitive method (sensitivity ranging from 89% to 90%) to confirm the presence of AERD and is used to achieve aspirin desensitization. However, significant and longer duration of bronchospasm are more likely to happen compared with bronchial and nasal challenge tests. In the United States, only the oral aspirin challenge test is available [32]. The oral test is carried out with placebo challenge, followed by 20–30 mg of aspirin which is increased (until a cumulative dose of 500 mg) at 2-h intervals. When patients who are suspected as having aspirin hypersensitivity do not show positive reactions after the final dose, 500 mg of aspirin can be administered (total cumulative dose of 1000 mg). If the patient has a history of severe hypersensitivity reactions (profound dyspnea and/or anaphylactic shock), the test is commenced with 10 mg of aspirin at longer intervals for patient safety [29]. This allows the challenge to be completed within 2–3 days. FEV1% predicted value is measured before each aspirin dose and every 30 min thereafter. The challenge is stopped if FEV1% falls by 20% of baseline or lower (a positive reaction). Oral challenge is preferred for the investigation of extrapulmonary or systemic symptoms of AERD. The threshold dose of aspirin that provokes a 20% FEV1 fall varies among patients and may represent bronchial sensitivity to CysLTs. Nasal aspirin challenge tests are also applicable, in which positivity is determined based on symptom scores and results of rhinomanometry and/or acoustic rhinometry after nasal instillation of lysine-aspirin solution [33]. The tests are safe, do not produce systemic reactions, but are not sensitive. They are recommended for patients with predominant nasal symptoms and for those in whom oral or inhalation tests are contraindicated because of the severity of their asthma. Patients with nasal problems, such as septal perforation or severe nasal blockade, are not suitable candidates (Table 1).

As *in vitro* testing, measurement of leukotriene which is released from peripheral blood leukocytes has been used for the diagnosis of AERD. However, the results of such studies are inconsistent [34]. There is still no useful *in vitro* test confirmed

Table 1. Characteristics of aspirin provocation tests in AERD.

Route	Starting dose	Cumulative dose	Frequency of dosing	Advantage	Disadvantage
Oral	27 mg	500 mg	4	Most sensitive Being able to assess extrabronchial symptoms	Not possible in patients with uncontrolled asthma (FEV1% should be at least 70% of predicted value) Probability of severe bronchospasm or anaphylaxis Long duration Occurrence of silent desensitization
Bronchial	0.18 mg	218 mg	8	Less probability of severe bronchospasm Rapid	Not possible in patients with uncontrolled asthma (FEV1% should be at least 70% of predicted value) Not possible in patients with only upper airway symptoms
Nasal	5 mg	75 mg	4	Safe Possible in patients with uncontrolled asthma	Low sensitivity Not possible in patients with nasal pathology Need for special equipment

FEV1: Forced expiratory volume in the first second.

Table 2. Diagnostic methods of AERD.

Confirmative diagnostic methods
Lysine–aspirin bronchoprovocation test
Oral aspirin provocation test
No reliable <i>in vitro</i> testing
Potential biomarkers
Serum periostin/DPP10 level
HLA DPB1*0301

DPP: Dipeptidyl-peptidase 10; HLA: human leukocyte antigen.

in the context of cross-reactive hypersensitivity reactions including AERD. The basophil activation test, which measures CD63 and/or CD203 expression on *in vitro* challenge, has been suggested for the *in vitro* diagnosis of AERD (especially for patients with anaphylaxis). The specificity and sensitivity of this test vary, and no firm conclusion on the reliability of this test in a clinical setting has been made [35]. Recent studies suggested potential biomarkers for predicting the phenotype of AERD. First, serum periostin level was significantly higher in AERD patients than in ATA patients, in which much higher levels were found in severe AERD patients with CRS [36]. Second, in parallel with the result of a GWAS study, significantly higher DPP10 level was noted in sera of AERD patients compared to ATA patients. Furthermore, the receiver operating curve analysis, which is applied to validate diagnostic accuracy of a test, suggested that DPP10 may be a significant serum biomarker for differentiating AERD from ATA groups [17,21] (Table 2). Nasal CysLTs and urine LTE4 metabolites were significantly higher in AERD group compared to the ATA group, which were also higher after an aspirin provocation test [37,38]. Therefore, LTE4 level in body fluids can be a consistent functional biomarker for diagnosing AERD compared to other types of asthma, including ATA patients and normal healthy controls. Recently, there have been a few studies showing high fractional exhaled nitric oxide levels in AERD patients compared to ATA group; however, these results are inconsistent among studies reported and further validation studies are needed [39].

5. Treatment and personalized medicine

Two essential components of AERD treatment are absolute avoidance of NSAIDs and pharmacological treatment according to the symptom severity of asthma and CRS. If indicated, aspirin desensitization, surgery, and novel treatment options with biologics can be applied [40,41].

Most AERD patients show similar upper and lower respiratory symptoms when exposed to various COX-1 inhibitors. There is extensive cross-reactivity among COX-1 inhibitors, while azapropazone, choline magnesium trisalicylate, and salsalate which are very weak inhibitors of COX-1 and COX-2 are well tolerated by the majority of AERD patients. Selective COX-2 inhibitors are generally well tolerated by most patients, but a few patients with unstable asthma (1–2%) react to selective COX-2 inhibitors [42]. Hypersensitivity reactions to selective COX-2 inhibitors are anecdotally known to occur in AERD patients with unstable asthma [43,44]. There is a report that 3 (2.9%) of 104 AERD patients developed positive reaction to oral challenge with etoricoxib [45]. In a systematic review, celecoxib exposure did not cause

significant difference in respiratory symptoms in AERD patients with stable asthma [46]. Therefore, the oral provocation test with alternative COX-2 inhibitor needs to be considered before prescribing them particularly for AERD patients with uncontrolled asthma.

Regarding pharmacologic treatment, most AERD patients have chronic asthma symptoms in a moderate-to-severe degree and should maintain step 4–5 treatments, including combination inhalers of medium/high dose of inhaled corticosteroid and long-acting β_2 -agonist with or without antimuscarinic agent according to the guideline [47]. Considering that CysLT overproduction is a key pathogenic mechanism, leukotriene modulators, including LTRAs and 5-LO inhibitors, are widely used in order to control CysLT-mediated upper and lower airway symptoms of AERD patients. They are prescribed as mono or add-on therapy to standard pharmacologic treatment. In clinical practice, LTRA is the most widely used drug for the treatment of AERD, especially in elderly AERD patients [48], because 5-LO inhibitor is available only in limited countries. The AERD patients treated with an LTRA generally show improvement in upper and lower airway symptoms, lung function, quality of life, asthma exacerbation, and less bronchodilator use [49]. According to control status, maintenance medications are increased (step up) or decreased (step down).

Aspirin desensitization can be considered when patients are refractory to conventional medications (especially for corticosteroid-dependent asthma) or need aspirin/NSAID maintenance to control other medical conditions, including coronary artery disease or chronic arthritis [40,41]. After an acute reaction (i.e. after inadvertent aspirin intake or diagnostic challenge), the refractory period develops and lasts 2–5 days. During this period, patients may take aspirin without any adverse symptoms. After that, aspirin may again precipitate an adverse reaction. However, by continuing administration of aspirin each day during the refractory period after reaction onset and thereafter for many weeks, months, or years, this state of tolerance can be maintained. This procedure is called desensitization. Several desensitization protocols that allow for completing the procedure within 3–5 days have been proposed. There have been several studies demonstrating that aspirin desensitization improves lung function and CRS symptoms. In addition, AERD patients who had nasal polypectomy, desensitization may improve both nasal symptoms and nasal polyp scores as well as the requirement for recurrent surgery [50,51]. There is no standardized protocol for aspirin desensitization; however, a maintenance aspirin dose of 650 mg twice daily for the first month and a lower dose of 325 mg twice daily, as symptoms are controlled, are recommended [40,51]. Aspirin desensitization can be beneficial for some patients with AERD associated with upper and lower airway inflammation but it should be adopted carefully considering serious adverse reactions, such as stomach pain or bleeding, during the maintenance period of aspirin desensitization.

Novel options with biologics are available to achieve more effective control of upper and lower airway symptoms of severe AERD patients. First, anti-IgE antibody therapy (omalizumab) improves upper and lower airway symptoms, quality of life, and nasal polyp score in severe, allergic asthma, including AERD [52,53]. A Japanese study demonstrated that anti-IgE

therapy for more than 6 months effectively reduced asthma exacerbation and CysLT levels in AERD patients, suggesting that omalizumab could suppress mast cell-mediated inflammation in the upper and lower airway mucosa of AERD patients [4]. However, substantial AERD patients are nonallergic and proportion of allergic subjects in AERD are not different from those in ATA. A few studies suggest that omalizumab also has therapeutic effects in patients with nonallergic asthma in which IgE localized in target tissues may play an important role [54,55]. Further study should conduct to find whether omalizumab is truly effective and which mechanism is involved for AERD. Second, a phase 2 clinical trial reported the benefit of mepolizumab in reducing the need for surgery in patients with severe, bilateral nasal polyps, including those with AERD [56]. Clinical trials of the anti-IL5 antibody reslizumab [57] and the anti-IL5 receptor antibody benralizumab in patients with severe eosinophilic asthma showed that the monoclonal antibodies effectively reduce asthma exacerbation, eosinophil counts, and asthmatic symptoms [58]. The effectiveness and safety of these biologics in AERD have not been systematically investigated. However, considering that eosinophils are more activated in the upper and lower airway mucosa of AERD and closely associated with severe CRS and asthma symptoms, anti-IL5 and anti-IL5 receptor antibodies may offer a promising treatment option. Given the role of PGD2 and its receptor, chemoattractant receptor homologue, expressed on Th2 cells (CRTH2) in the pathogenic mechanisms of AERD, a recent clinical trial showed that the CRTH2 antagonist OC000459 was effective in controlling eosinophilic inflammation [59], CRTH2 antagonists could be another potential treatment option to control airway inflammation in AERD patients (Figure 1).

In severe CRS patients with multiple nasal polyps and nasal passage obstruction, surgical procedures (polypectomy, functional endoscopic sinus surgery, or ethmoidectomy) are needed to relieve symptoms and to remove polypoid tissue from sinuses, although AERD patients seem to respond less well to surgical intervention.

6. Conclusion

The management of AERD should be preceded by detailed information on underlying asthma, and CRS/nasal polyps, which may affect the clinical course of AERD. The aspirin challenge test via the oral or bronchial route is a definitive method for diagnosing AERD. Guideline-based stepwise treatment is also effective for AERD patients. However, a considerable portion of AERD patients are not well controlled by pharmacologic treatment. Therefore, sinus surgery, aspirin desensitization, and biologic treatment are considerations according to the clinical manifestation of AERD.

7. Expert commentary

Initial AERD diagnosis is based on a history taking. However, some patients are not aware of reaction from aspirin or NSAIDs before provocation test and the others thought to be AERD show negative response to provocation test. To avoid these underdiagnosis and overdiagnosis of AERD, provocation test is useful. Three routes of provocation tests can be applicable, oral, bronchial (inhalation), and nasal. Although oral provocation test is still a gold standard for the diagnosis of AERD, substantial proportion of AERD patients have uncontrolled asthma. Therefore, oral challenge test has been replaced with bronchial/nasal challenge tests. Each test has relative advantage and disadvantage compared with others. Therefore, provocation test should be applied and interpreted according to the symptom and comorbidity of patients.

For AERD patients, all of aspirin or other NSAIDs can elicit hypersensitivity reaction. COX-2 inhibitors are mostly used safely but they can rarely cause reaction especially in patients with uncontrolled asthma. Therefore, safety of COX-2 inhibitors needs to be confirmed particularly in AERD patients with uncontrolled asthma before prescribing them.

Recent development of biologic agents targeting cytokines which underlie the pathogenesis of asthma may be of benefit for the treatment of AERD. AERD is a heterogeneous disease

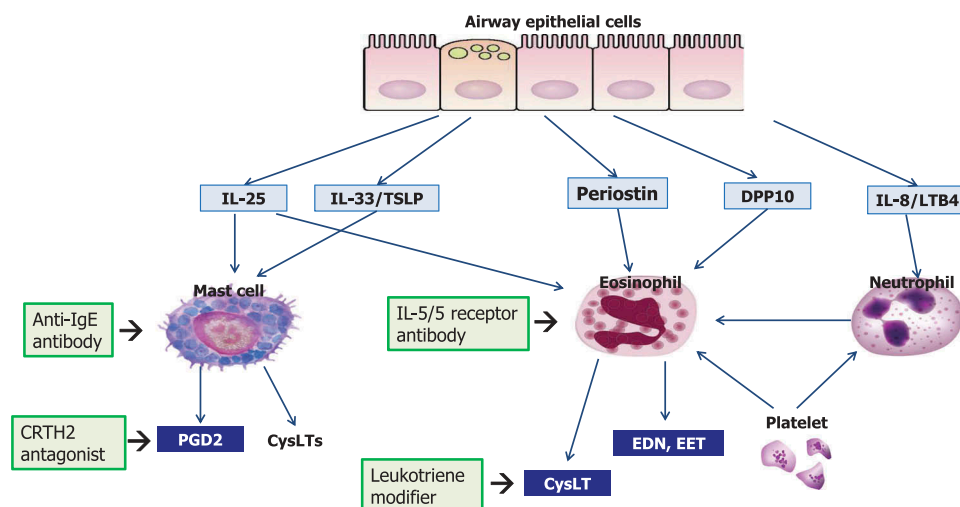


Figure 1. Potential targets in the pathogenic mechanisms of AERD.

CysLTs = cysteinyl leukotrienes; CRTH2 = chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells; EDN = eosinophil-derived neurotoxin; EET = eosinophil extracellular trap; DPP10 = dipeptidyl-peptidase 10; LTb4 = leukotriene B4; PGD2 = prostaglandin D2; TSLP = thymic stromal lymphopoietin.

and consists of different phenotypes. In addition to NSAIDs, atopic status, associated allergic disease, and other comorbid disease which may affect the clinical outcome of AERD should be taken into account. Treatment regimens should be optimized based on the severity of AERD.

8. Five-year view

Rapid growth of molecular genetic analysis will shed light on the genetic/epigenetic mechanisms underlying AERD. Safer and more reliable *in vitro* diagnostic tests to complement the risks of challenge tests will be validated in the clinical setting. Randomized clinical trials will clarify the efficacy of biologic agents for the treatment of AERD.

Key issues

- AERD is a major manifestation of NSAID hypersensitivity and usually associated with moderate to severe asthma with CRS/nasal polyps. It is mainly derived from arachidonic acid dysregulation (CysLT overproduction with a reduction in PGE₂), and activated eosinophils (with activated platelets) and mast cells. Major genetic/epigenetic mechanisms are dysregulation of genes involved in the 5-LO/15-LO pathways and eosinophil activation, including *CCR3* and *CRTH2*, as well as HLA DPB1*0301.
- The diagnosis of AERD can be established with aspirin provocation testing via the oral, bronchial, and nasal route and a history of adverse reactions to NSAID/aspirin. Novel biomarkers, such as serum periostin and DPP10, are under investigation to increase diagnostic value.
- Treatment options include absolute avoidance of COX-1 inhibitors, pharmacologic treatment, and aspirin desensitization if indicated. Besides standard pharmacological treatment (including LTRA), biologics, including anti-IgE (omalizumab) and anti-IL5 (mepolizumab, reslizumab) and anti-IL5 receptor antibodies (benralizumab) may offer treatment options for severe AERD patients with CRS. Considering heterogeneity in AERD, evaluation of AERD phenotypes will be essential for improving clinical outcome and for achieving the future precision medicine in the management of AERD.

Funding

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI16C0992).

Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy*. 2013;68(10):1219–1232.
- **This review provides practical methods in the diagnosis and management of patients with NSAID hypersensitivity including AERD.**
2. Le Pham D, Lee JH, Park HS. Aspirin-exacerbated respiratory disease: an update. *Curr Opin Pulm Med*. 2017;23(1):89–96.
3. Bochenek G, Kuschill-Dziurda J, Szafraniec K, et al. Certain subphenotypes of aspirin-exacerbated respiratory disease distinguished by latent class analysis. *J Allergy Clin Immunol*. 2014;133(1):98–103.
- **This article demonstrated four different classification of AERD based on a Polish cohort.**
4. Hayashi H, Mitsui C, Nakatani E, et al. Omalizumab reduces cysteinyl leukotriene and 9alpha,11beta-prostaglandin F₂ overproduction in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2016;137(5):1585–1587.
- **The study demonstrated the efficacy of omalizumab for the treatment of AERD patients through cysteinyl leukotrienes-involved mechanism.**
5. Rajan JP, Wineinger NE, Stevenson DD, et al. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: a meta-analysis of the literature. *J Allergy Clin Immunol*. 2015;135(3):676–681.
6. Blanca-Lopez N, Haroun-Diaz E, Ruano FJ, et al. Acetyl salicylic acid challenge in children with hypersensitivity reactions to nonsteroidal anti-inflammatory drugs differentiates between cross-intolerant and selective responders. *J Allergy Clin Immunol Pract*. 2017;10. DOI:10.1016/j.jaip.2017.08.029
7. Johns CB, Laidlaw TM. Elevated total serum IgE in nonatopic patients with aspirin-exacerbated respiratory disease. *Am J Rhinol Allergy*. 2014;28(4):287–289.
8. Lee JY, Kim HM, Ye YM, et al. Role of staphylococcal superantigen-specific IgE antibodies in aspirin-intolerant asthma. *Allergy Asthma Proc*. 2006;27(5):341–346.
9. Choi JH, Kim JH, Park HS. Upper airways in aspirin-exacerbated respiratory disease. *Curr Opin Allergy Clin Immunol*. 2015;15(1):21–26.
- **This review summarized recent publications of CRS and nasal polyps found in AERD patients.**
10. Sanak M. Eicosanoid mediators in the airway inflammation of asthmatic patients: what is new?. *Allergy Asthma Immunol Res*. 2016;8(6):481–490.
11. Cahill KN, Bensko JC, Boyce JA, et al. Prostaglandin D₂: a dominant mediator of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2015;135(1):245–252.
12. Jyothis SS, Eissa NT. Autophagy and role in asthma. *Curr Opin Pulm Med*. 2013;19(1):30–35.
13. Ueki S, Tokunaga T, Fujieda S, et al. Eosinophil ETosis and DNA Traps: a new look at eosinophilic inflammation. *Curr Allergy Asthma Rep*. 2016;16(8):54.
14. Ban GY, Pham DL, Trinh TH, et al. Autophagy mechanisms in sputum and peripheral blood cells of patients with severe asthma: a new therapeutic target. *Clin Exp Allergy*. 2016;46(1):48–59.
15. Liu T, Kanaoka Y, Barrett NA, et al. Aspirin-exacerbated respiratory disease involves a cysteinyl leukotriene-driven IL-33-mediated mast cell activation pathway. *J Immunol*. 2015;195(8):3537–3545.
16. Buchheit KM, Cahill KN, Katz HR, et al. Thymic stromal lymphopoietin controls prostaglandin D₂ generation in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2016;137(5):1566–1576.
17. Park H, Choi Y, Jung CG, et al. Potential biomarkers for NSAID-exacerbated respiratory disease. *Mediators Inflamm*. 2017;8. DOI:10.1155/2017/8160148
- **This article summarized potential diagnostic biomarkers including lipid mediator, cellular and cytokine markers, and genetic markers for predicting the phenotype of AERD.**
18. Choi JH, Lee KW, Oh HB, et al. HLA association in aspirin-intolerant asthma: DPB1*0301 as a strong marker in a Korean population. *J Allergy Clin Immunol*. 2004;113(3):562–564.

- **This study first demonstrated that HLA DPB1*0301 is a strong gene marker for the phenotype of AERD.**
- 19. Kim SH, Oh JM, Kim YS, et al. Cysteinyl leukotriene receptor 1 promoter polymorphism is associated with aspirin-intolerant asthma in males. *Clin Exp Allergy*. 2006;36(4):433–439.
- **This polymorphism was found in a Korean population, which was not reproduced in other ethnic country.**
- 20. Losol P, Palikhe NS, Lee JW, et al. Association of P2RY12 polymorphisms with eosinophil and platelet activation in patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2015;114(5):423–424.
- 21. Kim SH, Choi H, Yoon MG, et al. Dipeptidyl-peptidase 10 as a genetic biomarker for the aspirin-exacerbated respiratory disease phenotype. *Ann Allergy Asthma Immunol*. 2015;114(3):208–213.
- 22. Dahlin A, Weiss ST. Genetic and epigenetic components of aspirin-exacerbated respiratory disease. *Immunol Allergy Clin North Am*. 2016;36(4):765–789.
- 23. Cheong HS, Park SM, Kim MO, et al. Genome-wide methylation profile of nasal polyps: relation to aspirin hypersensitivity in asthmatics. *Allergy*. 2011;66(5):637–644.
- 24. Cahill KN, Raby BA, Zhou X, et al. Impaired E prostanoide2 expression and resistance to prostaglandin E2 in nasal polyp fibroblasts from subjects with aspirin-exacerbated respiratory disease. *Am J Respir Cell Mol Biol*. 2016;54(1):34–40.
- 25. Yoo HS, Shin YS, Liu JN, et al. Clinical significance of immunoglobulin E responses to staphylococcal superantigens in patients with aspirin-exacerbated respiratory disease. *Int Arch Allergy Immunol*. 2013;162(4):340–345.
- 26. Laidlaw TM, Kidder MS, Bhattacharyya N, et al. Cysteinyl leukotriene overproduction in aspirin-exacerbated respiratory disease is driven by platelet-adherent leukocytes. *Blood*. 2012;119(16):3790–3798.
- 27. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIAE Investigators. European network on aspirin-induced asthma. *Eur Respir J*. 2000;16(3):432–436.
- 28. Ledford DK, Wenzel SE, Lockey RF. Aspirin or other nonsteroidal inflammatory agent exacerbated asthma. *J Allergy Clin Immunol Pract*. 2014;2(6):653–657.
- 29. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy*. 2007;62(10):1111–1118.
- 30. Lee RU, Stevenson DD. Aspirin-exacerbated respiratory disease: evaluation and management. *Allergy Asthma Immunol Res*. 2011;3(1):3–10.
- 31. White A, Ludington E, Mehra P, et al. Effect of leukotriene modifier drugs on the safety of oral aspirin challenges. *Ann Allergy Asthma Immunol*. 2006;97(5):688–693.
- 32. Dursun AB, Woessner KA, Simon RA, et al. Predicting outcomes of oral aspirin challenges in patients with asthma, nasal polyps, and chronic sinusitis. *Ann Allergy Asthma Immunol*. 2008;100(5):420–425.
- 33. Miller B, Mirakian R, Gane S, et al. Nasal lysine aspirin challenge in the diagnosis of aspirin - exacerbated respiratory disease: asthma and rhinitis. *Clin Exp Allergy*. 2013;43(8):874–880.
- 34. Pierzchalska M, Mastalerz L, Sanak M, et al. A moderate and unspecific release of cysteinyl leukotrienes by aspirin from peripheral blood leucocytes precludes its value for aspirin sensitivity testing in asthma. *Clin Exp Allergy*. 2000;30(12):1785–1791.
- 35. De Weck AL, Sanz ML, Gamboa PM, et al. Nonsteroidal anti-inflammatory drug hypersensitivity syndrome: a multicenter study. II. Basophil activation by nonsteroidal anti-inflammatory drugs and its impact on pathogenesis. *J Investig Allergol Clin Immunol*. 2010;20(1):39–57.
- 36. Kim MA, Izuhara K, Ohta S, et al. Association of serum periostin with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2014;113(3):314–320.
- 37. Ban GY, Cho K, Kim SH, et al. Metabolomic analysis identifies potential diagnostic biomarkers for aspirin-exacerbated respiratory disease. *Clin Exp Allergy*. 2017;47(1):37–47.
- 38. Choi GS, Kim JH, Shin YS, et al. Eosinophil activation and novel mediators in the aspirin-induced nasal response in AERD. *Clin Exp Allergy*. 2013;43(7):730–740.
- 39. Jerschow E, Ren Z, Hudes G, et al. Utility of low-dose oral aspirin challenges for diagnosis of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2016;116(4):321–328.
- 40. Pham DL, Kim JH, Trinh TH, et al. What we know about nonsteroidal anti-inflammatory drug hypersensitivity. *Korean J Intern Med*. 2016;31(3):417–432.
- 41. Buchheit KM, Laidlaw TM. Update on the management of aspirin-exacerbated respiratory disease. *Allergy Asthma Immunol Res*. 2016;8(4):298–304.
- **This article reviews comprehensive management strategy for AERD.**
- 42. Kim YJ, Lim KH, Kim MY, et al. Cross-reactivity to acetaminophen and celecoxib according to the type of nonsteroidal anti-inflammatory drug hypersensitivity. *Allergy Asthma Immunol Res*. 2014;6(2):156–162.
- 43. Baldassarre S, Schandene L, Choufani G, et al. Asthma attacks induced by low doses of celecoxib, aspirin, and acetaminophen. *J Allergy Clin Immunol*. 2006;117(1):215–217.
- 44. Munoz-Cano R, Bartra J, Vennera MC, et al. Asthmatic reaction induced by celecoxib in a patient with aspirin-induced asthma. *J Investiq Allergol Clni Immunol*. 2009;19(1):75–76.
- 45. Koschel D, Weber CN, Hoffken G. Tolerability to etoricoxib in patients with aspirin-exacerbated respiratory disease. *J Investiq Allergol Clni Immunol*. 2013;23(4):275–280.
- 46. Morales DR, Lipworth BJ, Guthrie B, et al. Safety risks for patients with aspirin-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: meta-analysis of controlled clinical trials. *J Allergy Clin Immunol*. 2014;134(1):40–45.
- 47. Global initiative for asthma [Internet]. 2017. GINA report, global strategy for asthma management and prevention. [cited 2017 Oct 9]. Available from: www.ginasthma.org.
- 48. Trinh HK, Ban GY, Lee JH, et al. Leukotriene receptor antagonists for the treatment of asthma in elderly patients. *Drugs Aging*. 2016;33(10):699–710.
- 49. Dahlen SE, Malmstrom K, Nizankowska E, et al. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med*. 2002;165(1):9–14.
- 50. Cho KS, Soudry E, Psaltis AJ, et al. Long-term sinonasal outcomes of aspirin desensitization in aspirin exacerbated respiratory disease. *Otolaryngol Head Neck Surg*. 2014;151(4):575–581.
- 51. Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2003;111(1):180–186.
- 52. Li J, Kang J, Wang C, et al. Omalizumab improves quality of life and asthma control in Chinese patients with moderate to severe asthma: a randomized phase III study. *Allergy Asthma Immunol Res*. 2016;8(4):319–328.
- 53. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2013;131(1):110–116.
- 54. Garcia G, Magnan A, Chiron R, et al. A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma. *Chest*. 2013;144(2):411–419.
- 55. Pillai P, Chan YC, Wu SY, et al. Omalizumab reduces bronchial mucosal IgE and improves lung function in non-atopic asthma. *Eur Respir J*. 2016;48(6):1593–1601.
- 56. Gevaert P, Van Bruene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol*. 2011;128(5):989–995.
- 57. Farne HA, Wilson A, Powell C, et al. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev*. 2017;9:CD010834.
- 58. Park HS, Kim MK, Imai N, et al. A phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan. *Int Arch Allergy Immunol*. 2016;169(3):135–145.
- 59. Pettipher R, Hunter MG, Perkins CM, et al. Heightened response of eosinophilic asthmatic patients to the CRTH2 antagonist OC000459. *Allergy*. 2014;69(9):1223–1232.