



Invited Review Article

Aspirin-exacerbated respiratory disease (AERD): Current understanding of AERD

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ABSTRACT

The characteristics in AERD are severe adult-onset asthma, eosinophilic rhinosinusitis with nasal polyposis, and CysLT overproduction. The cause of AERD have remained unclear, however the decrease in the production of PGE₂ caused by the reduction in COX-2 activity is considered to main pathological mechanism of AERD. The mast cell activation and the interaction between platelets and granulocytes are lead to the CysLT overproduction and severe eosinophilic inflammation. The ongoing activation of mast cells is important key pathogenesis in not only stable AERD but exacerbated AERD by aspirin and NSAIDs. In recent years, type 2 inflammation caused by ILC2 activation in patients with AERD have been attracting attention. Omalizumab is effective option for AERD via suppression of mast cell activation and CysLT overproduction. Dupilumab improves sinus symptoms especially in patients with AERD. In near future, anti-platelet drug, CRTH2 antagonist, and anti-TSLP antibody may be useful candidates of therapeutic options in patients with AERD. Copyright © 2019, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access

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Introduction and definition

Aspirin-exacerbated respiratory disease (AERD) is caused not by an allergic reaction to aspirin but by a non-allergic hypersensitivity (intolerance) that produces severe respiratory symptoms (congested nose, nasal discharge, and asthma attacks) caused by nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, that inhibit cyclooxygenase (COX), a synthetic enzyme of prostaglandins (PGs).^{1–3} A hypersensitivity reaction in AERD is more frequently induced by NSAIDs that have a stronger COX-1 inhibitory activity. In contrast, a selective COX-2 inhibitor, such as celecoxib, can be safely used in patients with AERD.^{3–5} From these findings, it is concluded that the hypersensitivity reaction in AERD is caused by a COX-1 inhibition.^{1–5}

Epidemiological and clinical findings

AERD is rare among children. Frequency of AERD is ~5–10% of patients with adult-onset asthma,^{2,3,6,7} and the ratio of male and

female patients is 1:2.⁶ Usual patients with AERD have a severe asthma; therefore, the percentage of patients with AERD among asthma is high at specialist hospital, whereas it is less than 5% at general clinics.⁷ According to a European-wide study, the average age of AERD onset is 35 years,⁸ and according to studies in the US and Japan, it is 36 years.⁹ Namely, people in their 20s–40 s tend to develop AERD. Familial AERD has been reported in 1–2% of patients with AERD. Differences in the percentage of patients with AERD among races and regions have not been reported. The typical clinical features of AERD are as follows. The type of asthma in AERD is a non-atopic or weakly atopic constitution,¹⁰ and their almost all asthma onset in AERD is after adolescence.⁸ Patients with severe asthma account for more than half of patients with AERD.^{8,9} They tend to develop a persistent airflow obstruction which minimally improves after the inhalation of a β_2 agonist.¹¹ As explained, AERD is a typical intractable adult-onset asthma.^{12,13} In particular, non-atopic asthma in female patients with AERD tends to become intractable.¹⁴ However, there are some (~10%) patients whose symptoms are mild and such patients only develop asthma attacks when they take NSAIDs. The mechanisms of intractable AERD have remained unclear.^{1–3}

A severe nasal obstruction, nasal discharge, and asthma exacerbation are induced by usual dose of NSAIDs in patients with AERD. They often show facial flushing and conjunctival reddening

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derived from histamine overproduction. GI symptoms (abdominal pain, nausea, and diarrhea), chest pain,¹⁵ itching, skin rash¹⁶ and urticaria are sometimes observed in a third of patients with AERD. The hypersensitivity reaction in AERD appears within 1 h from ingestion of NSAIDs. The appearance of NSAIDs-hypersensitivity symptom is sometimes delayed when slow-releasing tablets or transdermal patches are used.

The most important characteristics of clinical feature in AERD is eosinophilic rhinosinusitis with nasal polyposis that may lead to hyposmia.² More than half of adult patients with moderate-severe asthma who have nasal polyposis complicated with AERD. Nasal symptoms (particularly hyposmia) generally develop several years before the onset of AERD. Currently, the symptoms of asthma are often stabilized by inhaled corticosteroid (=ICS) therapy; however, symptoms other than those in the lower respiratory tract become noticeable.² In recent years, eosinophilic otitis media, eosinophilic enteritis, and variant angina-like chest pain have been observed in more than half, ~30%, and 10–20% of patients with AERD, respectively.² Peripheral blood eosinophilia is more prominent in patients with moderate-severe AERD than in those with aspirin-tolerant asthma (ATA).

Ten to 20% of patients with AERD show a hypersensitivity reaction (mainly, coughing) to several kinds of mint and toothpaste containing them.² The mechanism for this is unclear; however, it is considered that the chemical structure of mint¹⁷ is similar to that of salicylates. It was previously reported that patients with AERD show a hypersensitivity reaction to colorings (such as tartrazine), additives, and natural salicylates contained in fruits and vegetables. However, the symptoms of asthma do not significantly worsen when patients orally ingest them in typical amounts and the proof of the benefit of avoiding them is insufficient.¹⁸ Note that the prompt administration of drugs (inhalation drugs¹⁹ and liquid drugs) containing additives (particularly, parabens and metabisulfate) may induce a hypersensitivity reaction in patients with unstable AERD. Some spices contain high contents of natural salicylates, the intake of which may worsen symptoms in patients with AERD.

Causes and pathogenetic mechanism of AERD

Several genetic studies on aspirin hypersensitivity have been performed to detect the genetic predisposition to AERD and to gain insight into the phenotypic diversity.^{20–22} However, familial AERD is rare,³ and no strong genetic basis has been observed.

There is no relationship between the past history of NSAID administration and the onset of AERD. As the pathogenic mechanism, autoimmune mechanism,²³ chronic viral infection,²⁴ and an allergic reaction to the superantigen of *Staphylococcus aureus*²⁵ have been considered. However, none of them are based on substantial grounds. The reasons why AERD is acquired (not congenital) or easily has the complication of eosinophilic rhinosinusitis have remained unclarified.

Typical pathological conditions

There are three typical pathological conditions of AERD: 1) severe asthma, 2) eosinophilic rhinosinusitis, and 3) cysteinyl leukotriene (CysLT) overproduction.^{26–30}

The urinary concentration of leukotriene E₄ (LTE₄), a stable metabolic product of cysteinyl leukotriene (CysLT), is 3–5-fold higher in patients with stable AERD than in patients with stable ATA (Fig. 1a).²⁹ The urinary LTE₄ concentration significantly decreases after an endoscopic nasal surgery of nasal polyposis (Fig. 1b).²⁹ The urinary LTE₄ concentration increases 2–30-fold during aspirin provocation test.^{26–30} Other typical pathological

conditions are an imbalance of eicosanoids and decreases in the production of the anti-inflammatory mediator, prostaglandin E₂ (PGE₂)³¹ and lipoxin (Fig. 2).³² The decrease in the production of PGE₂ caused by the reduction in COX-2 activity,³³ especially the attenuation of PGE₂ receptor subtype 2 (EP2) stimulation,³⁴ is considered to be related to the three above-mentioned typical pathological conditions of AERD. However, there have been no animal models of AERD, and *in vitro* specific reactions have not been confirmed thus far. The reason for the acquired (not congenital) imbalance of eicosanoids has not been clarified.^{1–3} In addition, the following are still unknown: 1) whether the imbalance of eicosanoids (Fig. 2) is observed throughout the body or only in the respiratory tract, 2) which cells show a hypersensitivity reaction to COX-1 inhibitors, and 3) why patients show a hypersensitivity reaction to even a small amount of aspirin.

Involvement of platelets

Platelets are crucially involved in development of allergic diseases, including bronchial asthma. Platelets in asthmatics are more activated than those in healthy individuals. Platelets are considered to be involved in the development of AERD because 1) AERD is induced after the administration of ≤100 mg of aspirin (a small amount of aspirin that mainly inhibits COX-1 in platelets), 2) there is a refractory period of 3–7 days after the administration of aspirin³⁵ (this refractory period is specific to AERD and almost corresponds to the lifetime of platelets), 3) patients with AERD are sensitive to COX-1 inhibitors but tolerant to COX-2 inhibitors (among the cells in the human body, only platelets contain COX-1 alone). The group of Laidlaw and Boyce³⁶ and Mitsui *et al.*³⁷ reported the specific activation of platelets as well as the frequent adhesion with granulocytes and platelets in peripheral blood and the respiratory tract of patients with AERD. Their findings correspond reasonably well to our hypothesis. These phenomena are not observed in patients with severe ATA or chronic eosinophilic pneumonia.³⁷ The activated platelets and adhesion molecules such as P selectin, lead to the adhesion of platelets and inflammatory granulocytes or respiratory epithelium. The interaction between platelets and granulocytes is considered to lead to the overproduction of CysLT and severe eosinophilic inflammation (Fig. 3).³⁷ However, no significant change in the platelet activation marker is observed during aspirin provocation test.³⁶ Very recently, Laidlaw *et al.* reported that P2Y₁₂ receptor antagonist (prasugrel) did not significantly attenuate AERD symptoms.³⁸

Role of mast cells

During aspirin reactions, many mediators are released including CysLT, tryptase, histamine, and prostaglandin D₂ (PGD₂) suggesting mast cell activation.^{16,39–42} Concentration of PGD₂ level, which is a marker of mast cell activation, is significantly high in their sputum,⁴³ urine⁴⁴ and exhaled breath condensate⁴⁵ in patients with stable AERD, even in those using ICS. Single bronchial inhalation of sodium cromoglycate (a mast cell stabilizer) rapidly improve their pulmonary functions especially in patients with stable AERD (Fig. 4).⁴⁶ On the basis of these findings, the ongoing activation of mast cells is one of the characteristics of pathogenesis in not only stable AERD but also exacerbated AERD by aspirin.⁴⁷

During oral aspirin challenge test, urinary level of prostaglandin D₂ metabolite (PGD₂M) levels significantly increase. Because there is a positive correlation between the urinary LTE₄ concentration and PGD₂M concentration, the aspirin induced hypersensitive reactions are mainly caused by mast cells.^{41,42} Both aspirin induced reaction and acute allergic reaction (anaphylaxis) via immunoglobulin E (IgE) might be similar mechanism.⁴² However, in the

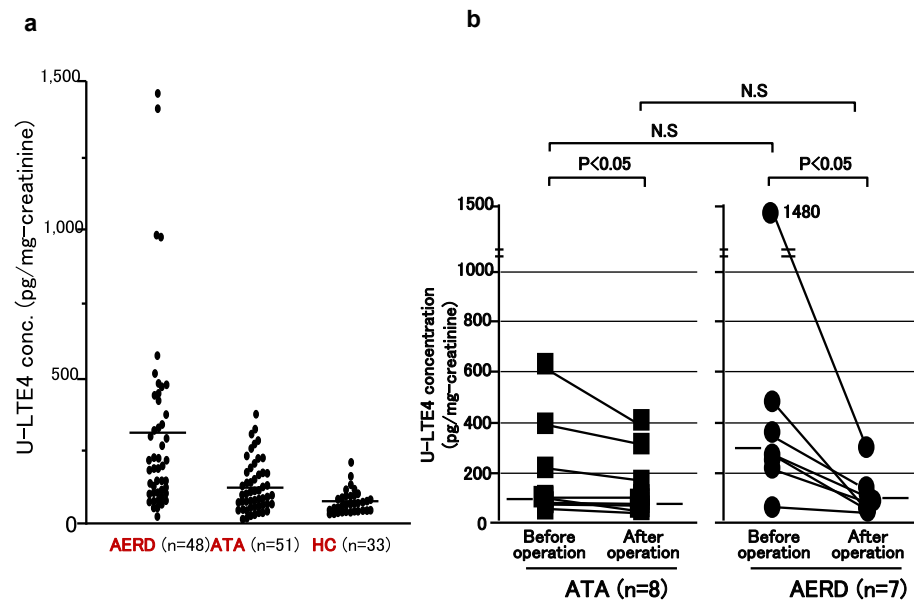


Fig. 1. (a) The urinary LTE4 concentration in patients with AERD and ATA during stable condition. Adapted from Kawagishi Y *et al.* J Allergy Clin Immunol 2002; 109: 936. (b) The urinary LTE4 concentration decreases significantly after the operation to remove nasal polyps. The concentration in some patients falls to within the normal range. Adapted from Higashi N *et al.* J Allergy Clin Immunol 2004;113:227.

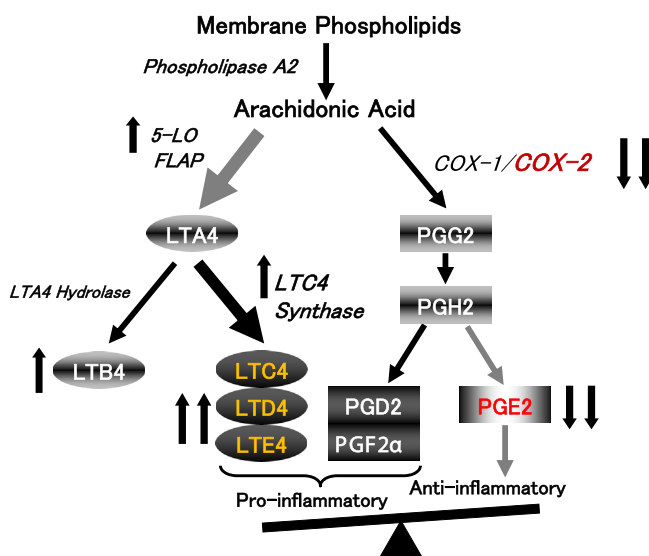


Fig. 2. Imbalance of arachidonic acid metabolites in patients with AERD (hypothesis). The COX-2 level decreases in patients with AERD and the production of endogenous PGE2 also decreases. With the addition of a COX-1 inhibitor, the amount of PGE2 further decreases, the suppression of 5-lipoxygenase (5-LO) activity disappears, and CysLT is overproduced.

case of IgE-anaphylaxis, PGD2 is dominant whereas CysLT is dominant in aspirin-induced reaction with AERD.⁴² The precise mechanism underlying the mutual activation of mast cells has not yet been clarified.

Involvement of basophils and innate lymphoid type 2 cells (ILC2)

Although, the main CysLT-producing cells are mast cells and basophils in human, basophils are not activated in the peripheral blood in patients with AERD in stable condition and during an aspirin challenge test.⁴⁸

In recent years, eosinophilic nasal polyps and type 2 inflammation caused by type 2 innate lymphoid cells (ILC2s) activation in patients with AERD have been attracting attention.⁴⁹ The involvement of ILC2 in the induction of AERD is expected because the pathological conditions caused by an increase in the number of eosinophils, rather than stimulation by an allergen, are the main symptoms. Recently, Eastman reported that ILC2s numbers significantly increased in nasal mucosal and decreased in blood during NSAID reactions in patients with AERD.⁵⁰ ILC2s could contribute to pathogenesis through production of type 2 cytokines.

TSLP induces type 2 cytokine generation by mast cells and ILC2s, and can activate eosinophils and basophils. Laidlaw and Boyce's group reported that mast cell-derived PGD2 is a major effector of type 2 immune responses driven by TSLP, and suggests that dysregulation of this innate system contributes significantly to the pathophysiology of AERD.⁴⁴

Common pathological conditions of eosinophilic nasal polyp and AERD: Decrease in COX-2 level (Fig. 5)

Figure 5 shows the relationship among the number of inflammatory cells and the levels of cytokines, chemokines, and various mediators in patients with chronic rhinosinusitis (CRS in Fig. 5), chronic rhinosinusitis with a nasal polyp (CRS + NP), and chronic rhinosinusitis with AERD complicated with a nasal polyp (CRS + NP + AERD). This figure summarizes the findings of previous reports. Patients with AERD have more severe pathological conditions than CRS + NP. It is considered that the pathomechanisms of AERD and eosinophilic nasal polyps are quantitatively different but qualitatively the same. This is consistent with the clinical findings for patients with AERD and those with ATA and a nasal polyp. The basic idea that can explain all the above phenomena is considered to be the decrease in COX level. On the basis of the results of analysis of COX activity in knockout mice^{51–54} and histopathological analysis of nasal polyps,^{25,55} a decrease in COX2 level can consistently explain the three typical pathological conditions of patients with AERD and eosinophilic rhinosinusitis described in Section Typical pathological conditions. Furthermore, the

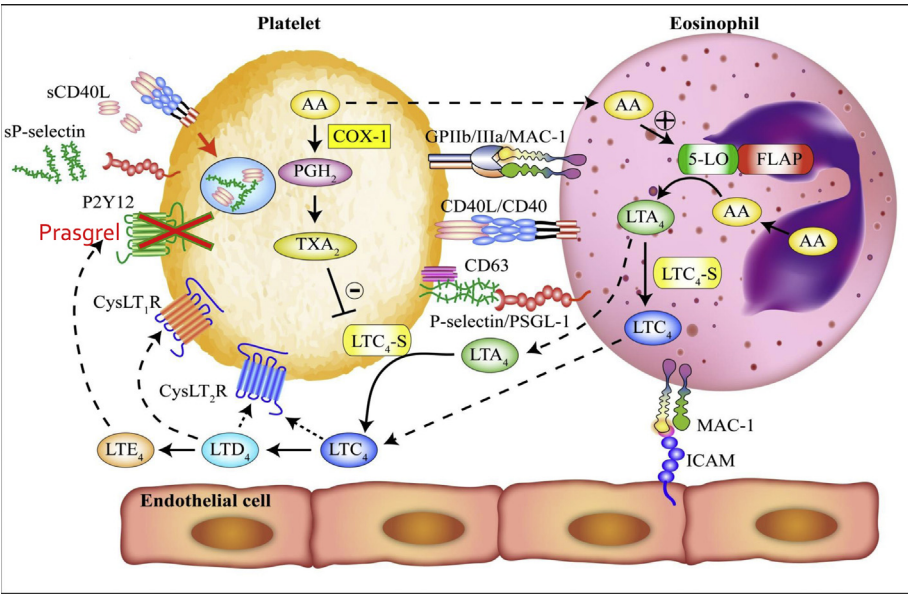


Fig. 3. New hypothesis of AERD development. Is the crosstalk between platelets and granulocytes the cause of AERD?

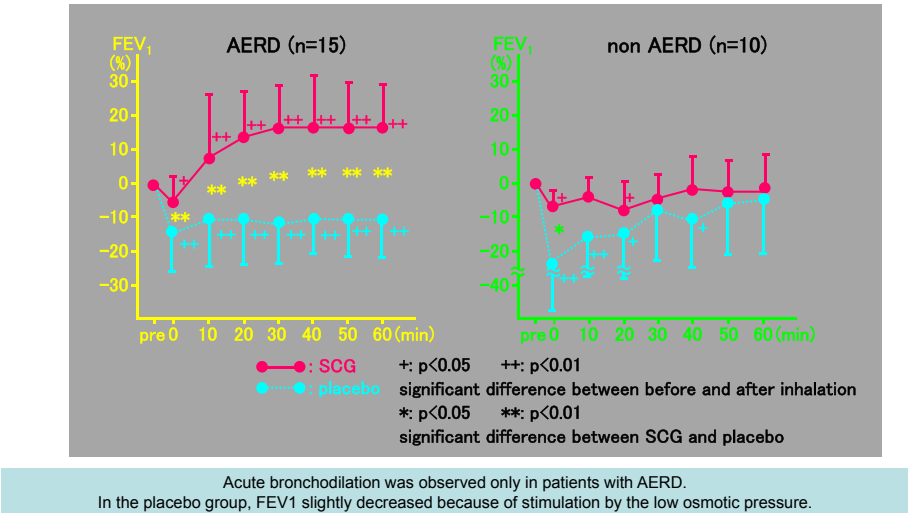


Fig. 4. Change in FEV1 in patients with AERD who inhaled Intal® (SCG) and a placebo group (patients who inhaled saline solution with the same osmotic pressure as that of SCG).

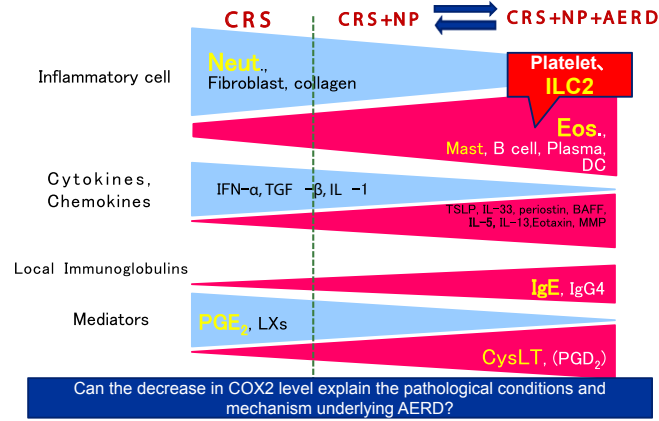


Fig. 5. Are CRS + NP and CRS + NP + AERD continuous pathological conditions? This figure shows a summary of the findings of past reports and our experience.

underlying mechanism is considered to be the attenuation in the EP2 receptor function (anti-inflammatory function) caused by the impaired production of endogenous PGE₂ owing to the decrease in COX2 level.^{34,56,57} The research group of Boyce demonstrated that PGE₂-1-synthesis-enzyme-deficient mice show pathological conditions similar to those of AERD and that the inflammatory symptoms can be improved by treatment with an EP2 receptor agonist.⁵¹ However, insufficient proof has been obtained thus far. In addition, the cells and tissues in which a decrease in COX2 level has a significant effect have not yet identified and the reason for the acquisition of AERD (not congenital) has not yet been determined. Hayashi *et al.* have recently reported the possibility that smoking, which induces COX-2 in the respiratory tract, inhibits the onset of AERD in humans, because people who quit smoking tend to develop asthma within 5 years of quitting and, among patients who smoke, the number of AERD patients is statistically significantly smaller than that of ATA patients.⁵⁸

Diagnosis method

Hypersensitivity to aspirin is caused by the mechanism of a non-allergic reaction. Therefore, general allergy tests (skin examination and blood tests) are not used to diagnose AERD.^{2,3,59,60} A drug lymphocyte stimulation test (DLST) using peripheral blood is also not helpful in diagnosis.² AERD is basically diagnosed by a medical interview and aspirin challenge test.^{2,3,59,60} In the medical interview, doctors should ask questions to patients to confirm the following three points.² ① History of the use of NSAIDs and any adverse events related to their use: the history of the use of NSAIDs before the onset of asthma should not be taken into consideration because patients develop hypersensitivity to NSAIDs after the onset of asthma. ② Presence of hyposmia: nasal polyps tend to develop in the vicinity of the ethmoid sinus in patients with AERD. Therefore, they tend to complain of hyposmia (~90% of patients) from an early stage of AERD, which can be transiently recovered by the administration of systemic steroids. ③ Histories of nasal polyps and rhinosinusitis and surgical history:

In addition, if a patient satisfies two or more items from among the following clinical backgrounds, in addition to the above three items, the patient is strongly suspected of having AERD. The clinical backgrounds include moderate or severe asthma, the onset of asthma after adolescence, a weakly atopic disposition, asthma with an intractable cough, and $\geq 10\%$ increase in peripheral eosinophilia.

The gold standard for making a definitive diagnosis is the aspirin oral challenge test.^{3,59,60} It is desirable to carry out the test at a specialized institution with experienced doctors when the symptoms of the patient are in a stable period. The details of the aspirin challenge test are given in references 3 and 60.

Specific therapies

Intravenous corticosteroids

We have pointed out in our previous reports that the rapid intravenous injection of steroids may cause a severe asthma attack.^{2,61} The chemical structure of steroids and endogenous steroids are insoluble in water. The steroids used for intravenous injection have the ester structure of phosphoric acid or succinic acid. Patients with AERD show a hypersensitivity reaction to the chemical structure of succinic acid steroids. Therefore, the rapid intravenous injection of succinate ester steroids should be avoided for patients with AERD. Also, the rapid intravenous injection of other types of steroids with several additives should therefore be avoided. Intravenous drip injection over at least 1–2 h is recommended.²

Cromolyn

It was demonstrated that cromolyn (Intal®), a mast cell stabilizer, is effective candidate for patients with unstable AERD.⁴⁶ The mechanism behind this is considered to be the continuous activation of mast cells in the respiratory tract of patients with AERD.

Anti-IgE

Omalizumab is very effective for AERD and acts rapidly.⁶² The mechanism behind this is the suppression of production of PGD₂ and CysLT overproduction rather than the attenuation of eosinophilic inflammation.⁶² Omalizumab suppresses mast cell activation in patients with intractable urticaria and is rapidly effective. It is also considered that omalizumab is effective as a mast cell stabilizer for patients with AERD. The current approach to treating intractable AERD is the use of omalizumab in addition to the drugs that the patient generally takes.

Anti-IL-4/13

Patients with AERD had stronger sinus inflammation at baseline compared with aspirin-tolerant patients with CRSwNP. Recently, Laidlaw reported that anti-IL-4/13 drug, Dupilumab significantly improved sinus symptoms including smell sense, in addition to improving asthma control and lung function especially in patients with AERD.⁶³ Larger studies are needed to confirm the efficacy.

Adrenaline

Adrenaline is effective for all types of NSAID-induced acute symptoms of patients with AERD.² This is because the pathological conditions, such as systemic vascular leakage, induced and the increased production of mediators are similar to the anaphylactic reactions via IgE.^{31,41,42}

Aspirin desensitization

Some patients with AERD have difficulty managing airway symptoms and are therefore candidates for aspirin desensitization and daily aspirin therapy.^{64,65} Aspirin desensitization, followed by aspirin treatment at a dose of 325–650 mg twice daily, is the one of therapeutic options for patients with AERD especially in US.⁶⁴ White's group claimed that most patients undergoing aspirin desensitization will have symptoms, but desensitization can be done safely and efficiently in an appropriately equipped outpatient setting.⁶⁶ Sanak and Nizankowska's group reported that beneficial effects of aspirin treatment on nasal and bronchial symptoms occurred only in the patients with AERD using double-blind, placebo-controlled study.⁶⁷ Recently, Cahill *et al.* demonstrated interesting mechanism of aspirin desensitization. They showed that aspirin therapy decreased urinary prostaglandin E, D₂ and thromboxane metabolite and increased urinary leukotriene E₄ levels in subjects with AERD.⁶⁸

Conclusion

The specific pathomechanism of AERD are not only mast cell activation, but platelet and ILC2 activation. Recent reports claim that anti-IgE treatment is strong candidate for intractable AERD patients via mast cell stabilization. In future, anti-platelet, anti-mast cell, and anti-ILC2 drugs may be useful options for AERD.

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Conflict of interest

The authors have no conflict of interest to declare.

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