



New concepts for the pathogenesis and management of aspirin-exacerbated respiratory disease

Esha Sehanobish, Mohammad Asad, and Elina Jerschow

Purpose of review

The purpose of this review is to provide a comprehensive summary of the current understanding of the pathogenesis of aspirin-exacerbated respiratory disease (AERD), and an update on its management.

Recent findings

Elevated levels of 15-oxo-eicosatetraenoic acid (15-Oxo-ETE), a newly described metabolite of arachidonic acid, have been identified in nasal polyps of AERD patients. In nasal polyps, activated basophils, and interleukin-5-receptor- α -positive IL-5R α^+ plasma cells are associated with more severe nasal polyposis in AERD. Alveolar monocyte-derived macrophages and their persistent proinflammatory activation were suggested as putative factors contributing to AERD. Although not AERD-specific, three biological agents are now available for the management of both nasal polyposis and asthma.

Summary

A newly downstream product of 15-lipoxygenase, 15-Oxo-ETE, was recently found to be significantly elevated in nasal polyps from AERD patients. This eicosanoid metabolite likely originates from an interplay between epithelial cells and mast cells. Nasal polyp basophils, IL-5R α^+ plasma cells, and alveolar macrophages were identified as important contributors to inflammation in AERD. Besides traditional aspirin desensitization and treatment for AERD management, several biologics for treatment of asthma are available, including three that have been approved for nasal polyposis. These biologic agents show variable rates of success in controlling AERD symptoms.

Keywords

15-oxo-eicosatetraenoic acid, aspirin-exacerbated respiratory disease, basophils, biologics, cyclooxygenase-1, IL-5R α^+ plasma cells, macrophages

INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) is a clinical syndrome characterized by asthma, nasal polyposis, and acute respiratory reactions to cyclooxygenase-1 (COX-1) inhibitors, including aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) [1]. Studies of AERD pathogenesis indicate that nasal polyps and aberrant arachidonic acid metabolism are at the core of this syndrome [1,2[■],3[■]]. Nasal polyps represent not only a mechanical obstruction but are also a major tissue locus of inflammation in AERD patients. Polyp growth is associated with a strong type 2 pro-inflammatory state characterized by high systemic levels of prostaglandin D₂ (PGD₂) and leukotriene E₄ (LTE₄), and low levels of anti-inflammatory eicosanoids, such as lipoxin A₄ [3[■],4–8]. When nasal polyps are surgically removed, these features are significantly reversed [2[■],3[■]]. AERD patients have a seemingly paradoxical

response to NSAIDs, as COX-1 inhibition in AERD causes a multifold increase in PGD₂ and LTE₄, instead of the expected decrease in PGD₂ and little change in LTE₄ levels. This discrepancy suggests dysregulation of arachidonic acid metabolism, leading to an aberrant eicosanoid profile.

The abnormal eicosanoid profile results from cells that generate eicosanoids and type 2 inflammation results from interactions between the immune and structural cells, including eosinophils, mast cells, innate lymphoid type 2 (IL2) cells,

Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, New York, USA

Correspondence to Elina Jerschow, MD, MS, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, New York, USA.

Tel: +1 718 405 8075; e-mail: ejerscho@montefiore.org

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KEY POINTS

- 15-Oxo-ETE, a newly identified downstream product of 15-LO, is significantly elevated in the nasal polyps from AERD patients.
- Basophils, IL-5R α^+ plasma cells, and macrophages were identified as important novel contributors to inflammation in AERD.
- Along with traditional aspirin desensitization and treatment for AERD management, several different biologics are now available for the treatment of asthma which includes three that have been approved for the treatment of nasal polyposis.

platelets, epithelial cells, and more recently identified basophils, macrophages, and interleukin-5-receptor- α -positive (IL-5R α^+) plasma cells [9^{••}, 10^{••}, 11^{••}]. Both eicosanoid metabolism and the cellular components of the characteristic inflammation are important for understanding the mechanism of AERD, and for development of new diagnostic and treatment approaches.

KEY EICOSANOIDS INVOLVED IN ASPIRIN-EXACERBATED RESPIRATORY DISEASE

AERD is associated with dysregulation of arachidonic acid metabolism that results in high levels of two major eicosanoids: cysteinyl leukotrienes (cysLTs) and prostaglandins. CysLTs are the 5-lipoxygenase (5-LO) catalyzed products of arachidonic acid. 5-LO oxidizes arachidonic acid in neutrophils, eosinophils, mast cells, and basophils to generate leukotriene A₄ (LTA₄) [12]. This unstable product is then converted to leukotriene C₄ (LTC₄) by the enzyme leukotriene C₄ synthase (LTC₄S). LTC₄ is then converted to two potent bronchoconstrictors leukotrienes D₄ (LTD₄) and E₄ (LTE₄) [13,14].

The overproduction of cysLTs is a characteristic feature of AERD [15]. Elevated levels of LTE₄ are observed at baseline and increase further after aspirin challenge in patients with AERD [16]. Compared to non-AERD controls, the bronchial tissues of AERD patients had positive staining for 5-LO in both mast cells and eosinophils [17,18]. Leukocytes such as neutrophils and monocytes lack LTC₄S and cannot convert LTA₄ to LTC₄ [19]. But platelets possess LTC₄S, which upon aggregating with leukocytes is capable of further metabolizing LTA₄ to cysLTs [19].

15-lipoxygenase (15-LO) is another enzyme involved in the metabolism of arachidonic acid. *ALOX15*, the gene encoding this protein, has been implicated in asthma and chronic rhinosinusitis

with nasal polyps [20,21]. A missense mutation in this gene resulting in a nonfunctional enzyme was found to protect from developing nasal polyps [22]. By comparing the transcriptional profile of nasal polyp cells of patients with AERD and chronic rhinosinusitis with nasal polyps (CRSwNP) using single-cell RNA sequencing, the levels of *ALOX15* were found to be higher in the nasal polyp tissue of AERD patients [23^{••}]. Stevens *et al.* identified a potential pathway contributing to the dysregulation of arachidonic acid via the 15-LO pathway by the synthesis of a downstream product called 15-oxo-eicosatetraenoic acid (15-Oxo-ETE) [23^{••}]. 15-Oxo-ETE is produced by conversion of arachidonic acid to 15-hydroxyeicosatetraenoic acid (15-HETE) by 15-LO, and then to 15-Oxo-ETE by hydroxyprostaglandin dehydrogenase [23^{••}].

Arachidonic acid is also metabolized by cyclooxygenase-1 (COX-1) to five main bioactive prostaglandins that are commonly implicated in AERD. These are prostaglandin D₂ (PGD₂), E₂ (PGE₂), F_{2 α} (PGF_{2 α}), prostacyclin (PGI₂), and thromboxane (TXA₂). PGD₂ is the dominant product of the arachidonic acid metabolism in mast cells [4]. The functions of PGD₂ are mediated through its interactions with the T-prostanoid (TP) receptor, D-prostanoid receptor 1 (DP1) and chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2). The levels of PGD₂ were found to be significantly higher in the sputum and urine of AERD patients compared to aspirin-tolerant asthma patients [24,25]. Various factors could contribute to the dysregulated production of PGD₂. Hematopoietic prostaglandin D synthase (hPGDS) is an enzyme required for the synthesis of PGD₂. AERD patients have a high number of eosinophils and mast cells in their nasal polyp tissues and gene expression analysis shows increased mRNA levels for hPGDS compared to control patients with asthma, leading to a higher production of PGD₂ [4,26,27]. Increased PGD₂ levels could be due to the high levels of cytokine thymic stromal lymphopoietin in the nasal polyp tissues of AERD patients compared to the aspirin-tolerant control patients (TSLP) [4,28].

In contrast to PGD₂, PGE₂ exerts anti-inflammatory effects in AERD and prevents airway obstruction. In AERD patients, it suppresses urinary LTE₄ increase upon aspirin challenge [29^{••},30]. Most of the anti-inflammatory functions of PGE₂ in the airways are exerted by its interactions with the E-prostanoid receptors 2 and 4 (EP2 and EP4), which activate phosphorylation of 5-LO. This blocks the activity of 5-LO and therefore reduces production of cysLTs [31]. PGE₂ exerts a brake on the production of cysLTs [29^{••},32]. Reduced production of PGE₂ has been observed in the bronchial fibroblasts and

epithelial cells from nasal polyps of AERD patients compared to the aspirin-tolerant asthma patients [33,34].

Lipoxins are oxygenated derivatives of arachidonic acid that are different from the other eicosanoids since they contain conjugated tetraene structures [35]. Following platelet-leukocyte interactions, platelet 12-lipoxygenase converts LTA₄ produced by leukocytes to lipoxins A₄ and B₄ [36]. In another pathway, 15-LO converts arachidonic acid to 15-HETE which is then converted to lipoxins by 5-LO [36].

In patients with AERD, reduced levels of lipoxins were observed at baseline in plasma and blood leukocytes compared to aspirin tolerant asthma patients [8]. Plasma lipoxin A₄ levels significantly increased after polyp removal by sinus surgery [3[°]]. AERD patients have higher levels of 15-LO, which converts arachidonic acid to lipoxin A₄ [23[°]]. 15-oxo-EETE, a downstream product of the 15-LO pathway, was also found to be elevated in AERD patients [23[°]]. It is possible that a preferential conversion to 15-oxo-EETE and not to lipoxins is a cause for the reduced expression of the latter in AERD patients [23[°]].

KEY CELLS INVOLVED IN ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Dysregulation of eicosanoids in AERD likely depends on the interactions between the cells involved in eicosanoid production and cells that respond to eicosanoid signaling.

Through several receptor signaling, leukotrienes activate mast cells that are highly abundant in nasal polyps of AERD patients [4,37]. Mast cells can be activated by TSLP through TSLP receptor, and especially in the presence of interleukin-33 (IL-33) [4]. Epithelial cells produce both TSLP and IL-33, which were detected in the nasal polyps of AERD patients [4,38–40]. Mast cell activation by TSLP and IL-33 results in high production of PGD₂ [4,41[°]]. In turn, PGD₂ recruits more eosinophils and other T2-pro-inflammatory cells, on which the PGD₂ receptor, CRTH2, is expressed [4,42,43]. These cells include innate lymphoid type-2 cells (ILC2). ILC2 is a subset of innate lymphoid cells that lack antigen-specific receptors. During aspirin-induced reactions in AERD patients, ILC2s are recruited to the nasal mucosa of AERD patients [44].

Although ILC2 lack a specific antigen receptor, two recent studies indicated a potential involvement of a cryptic or microbial antigen that induces local generation of IgE in nasal polyps [10[°],11[°]]. High basophil numbers and ongoing degranulation were observed in AERD patients compared to

CRSwNP [11[°]]. Basophils produce IL-4 and IL-13 cytokines, leading to IgE-class switching, mucus production, and impairment of epithelial barrier, all known to be dysregulated in nasal polyposis [45]. IgE is a potent activator of basophils that leads to degranulation in the nasal polyp tissue of AERD patients [46]. The mean number of basophils was significantly higher in AERD compared to the nasal polyps of patients with chronic rhinosinusitis with nasal polyps (CRSwNP) [11[°]]. Basophil presence in nasal polyps and their degree of degranulation as assessed by the presence of 2D7 granule content marker significantly correlated with greater CRSwNP severity, indicated by higher Lund-Mackay sinusitis scores, and lower lung function, measured by forced expiratory volume in 1 s (FEV1) [11[°]].

Another indicator of IgE involvement in AERD was confirmed by the greater presence of IL-5Rα⁺ plasma cells in nasal polyps of AERD patients than in patients with CRSwNP [10[°]]. In nasal polyps, higher IgE levels in the tissue were associated with a faster polyp recurrence, whereas higher IgG4 levels were associated with longer AERD duration [10[°]]. Expression of the IL-5 Receptor-α was enhanced on tissue plasma cells in AERD patients and was associated with the greater IgE and IgG4 levels [10[°]]. The authors concluded that IL-5 signaling affects differentiation and activation of IL-5Rα-expressing plasma cells, leading to local antibody production.

Another recent study indicated epigenetic reprogramming of macrophages in AERD [9[°]]. Haimel *et al.* described that macrophages in AERD produce an array of type 2 pro-inflammatory fatty acid metabolites [9[°]]. Upon stimulation with Ca²⁺ ionophore, alveolar-like monocyte-derived macrophages (aMDMs) from patients with AERD produced significantly more 5-LO-derived pro-inflammatory ‘metabolites and acylcarnitines than did aMDMs from healthy controls. In response to a pro-inflammatory challenge with LPS, these macrophages also showed upregulated expression of type 2 inflammatory chemokines (CXCL2 and CXCL8) and cytokines (IL-1B and TNFA) genes. These pro-inflammatory changes in AERD macrophages remained apparent for several days after stimulation with LPS, indicating a persistent metabolic and epigenetic reprogramming of macrophages as a potential mechanism of chronic type 2 inflammation. Finding elevated levels of acylcarnitines in macrophages of AERD patients suggested a more widely dysregulated fatty acid metabolism in AERD [9[°]].

Taken together, cellular interactions through eicosanoid signaling via specific receptors contribute to AERD features. Further work on defining their roles in AERD pathophysiology is needed to understand the mechanism of this syndrome.

UPDATES ON AERD MANAGEMENT

AERD patients suffer the burden of three conditions: asthma that is usually severe, recalcitrant nasal polyps with repeated sinus surgeries, and dangerous reactions to NSAIDs. The management of AERD usually involves multidisciplinary approach. A widely accepted treatment plan involves endoscopic sinus surgery (ESS), followed by aspirin desensitization and long-term aspirin maintenance treatment [47[■],48[■],49]. Bone remodeling is characteristic in AERD, and the inter-sinus sphenoid septum has a significantly increased thickness compared to non-AERD control groups [50[■]]. Therefore, a more extensive sinus surgery for AERD patients is frequently indicated, to allow better access for postoperative nasal irrigations with topical corticosteroids and a more favorable response to long-term aspirin treatment [48[■],51]. Although 8-week long aspirin treatment increased T2-markers in AERD patients, it notably decreased urinary PGD₂ metabolite (PGDM) levels [52]. Nevertheless, AERD symptoms remain uncontrolled on aspirin treatment in some patients [53,54]. In addition, in 14% to 20% of

aspirin-treated patients, the side effects of aspirin prevent long-term aspirin therapy [55,56].

Biologic treatments have become an important alternative for AERD. Currently, there are five biologics approved for eosinophilic or allergic asthma: omalizumab, mepolizumab, benralizumab, reslizumab, and dupilumab [57–61]. Out of these, three medications have been approved for treatment of chronic rhinosinusitis with nasal polyposis.

OMALIZUMAB

Omalizumab is a recombinant humanized anti-IgE monoclonal antibody that forms complexes with free IgE, blocking its interaction with mast cells and basophils [57]. In sixteen Japanese AERD patients, treatment with omalizumab for three months was associated with a significant reduction in LTE₄ and PGDM levels after aspirin challenge. Ten out of sixteen patients (62%) had a complete absence of clinical reactions to aspirin [62[■]]. This effect was comparable and even stronger than the effects of ESS, after which AERD patients exhibited significantly reduced levels of LTE₄, PGDM, and an

Table 1. Effects of monoclonal antibody treatments on eicosanoids levels and cellular components in AERD patients

	Mechanism of action	Effects on eicosanoids	Effects on cellular components	Clinical observations in AERD patients
Omalizumab	Omalizumab is an anti-IgE monoclonal antibody that blocks the interaction of IgE with mast cells and basophils [57,73].	In AERD, omalizumab inhibits and reduces the levels of uLTE ₄ and PGDM [62 [■]].	In allergic asthma, omalizumab increases eosinophil apoptosis [74].	Omalizumab reduces symptoms of hypersensitivity reactions induced by aspirin challenge [62 [■]]. Omalizumab benefits are notable in atopic AERD patients [63 [■]].
Mepolizumab	Mepolizumab is an anti-IL-5 antibody. It directly inhibits the IL-5 α -receptor signaling on basophils, eosinophils, mast cells, and epithelial cells [66 [■] ,75].	In AERD, mepolizumab reduces the levels of nasal PGDM and the uLTE ₄ [66 [■]].	Mepolizumab reduces the levels of peripheral eosinophils and basophils [66 [■]]. It also reduces local nasal IgE levels [66 [■]].	A subset of AERD patients with high IgE has little benefit from mepolizumab treatment [68 [■]].
Dupilumab	Dupilumab is a monoclonal antibody that inhibits the signaling by IL-4 and IL-13. It functions as an IL-4 α -receptor antagonist [58,76].	In AERD, dupilumab reduces uLTE ₄ levels [71 [■]].	In patients with asthma and chronic rhinosinusitis with nasal polyps, there is a transient increase in the level of blood eosinophil levels initially but then they decrease to below baseline levels over time [77 [■]]. Dupilumab significantly decreases systemic IgE levels in patients with nasal polyps, including those with AERD [78 [■]].	Treatment with dupilumab resulted in greater clinical improvement and higher rates of compliance in AERD patients, compared to anti-IgE treatment with omalizumab, and anti-IL5R treatment with mepolizumab [68 [■] ,72 [■]].

IL-13, interleukin-13; IL-4, interleukin-4; IL-5, interleukin-5; PGDM, prostaglandin D₂ metabolite; uLTE₄, urinary leukotriene E₄.

improved tolerance of aspirin, with more than a third of the patients not reacting to it clinically [3[■]]. Omalizumab was most beneficial to AERD patients with atopy [63[■]].

MEPOLIZUMAB

Mepolizumab is a monoclonal antibody against IL-5 [61,64]. It has benefited patients with eosinophilic asthma as well as patients with CRSwNP [61,65[■]]. In AERD patients, its benefit seems to be related not only to a direct blockade of IL-5, but also to a significant decrease in systemic levels of PGDM, LTE₄, and local nasal IgE [66[■]]. These changes are likely due to the direct inhibition of IL-5 α -receptor signaling on eosinophils, basophils, mast cells, and epithelial cells [66[■]]. Nevertheless, not all AERD patients benefit from mepolizumab and some experience recurrence of the symptoms and break-through eosinophilia despite their compliance with therapy [67[■]]. Notably, AERD patients with the lack of therapeutic benefit to mepolizumab had high baseline eosinophil or IgE levels [67[■],68[■]].

DUPILUMAB

Dupilumab is a fully human monoclonal antibody specific for the IL-4 receptor α -subunit that inhibits signaling by IL-4 and IL-13 cytokines [58,69]. Dupilumab therapy resulted in a significantly greater benefit in nineteen AERD patients (eight enrolled into dupilumab treatment group and eleven in placebo) compared to non-AERD patients with nasal polyps [70[■]]. In this study, more severe disease was evident in AERD patients at baseline compared to non-AERD CRSwNP controls. However, all of the studied outcomes showed significant improvement, including reduction in symptoms of sinusitis, nasal polyp scores, improved sense of smell, and a significant increase in forced respiratory volume in 1 s (FEV1) after 16 weeks of dupilumab treatment compared to placebo [70[■]]. In another study, dupilumab's clinical benefit in AERD patients was associated with a significant decrease in LTE₄ levels after two months of treatment [71[■]].

Transitioning to dupilumab therapy of AERD patients with high baseline serum IgE levels and an inadequate response to antiinterleukin-5 agents resulted in a significant improvement in sinonasal and asthma outcomes [68[■]]. In one center study, dupilumab therapy resulted in greater clinical improvement and higher rates of compliance in AERD patients, followed by the anti-IgE treatment with omalizumab, and anti-IL-5R treatment with mepolizumab [72[■]]. Table 1 summarizes the

mechanism of action of these biologics and their effects on eicosanoids and cellular components in AERD patients [73–76,77[■],78[■]].

CONCLUSION

AERD is one of the more severe phenotypes of eosinophilic asthma with nasal polyposis [73]. With the emergence of biologics, new insights into the mechanism and treatment of AERD have become available. The connection between changes in immune and structural cell activation, eicosanoid levels, and therapeutic benefits became more noticeable and could likely lead to the development of new biomarkers that may improve AERD diagnosis and disease activity monitoring. For example, a decrease in PGD₂ and LTE₄ levels that lead to the lack of hypersensitivity reaction to aspirin in patients treated with omalizumab has been observed. A decrease in LTE₄ and IgE in patients treated with dupilumab was associated with improvement in the sinonasal and asthma outcome scores. In addition, AERD patients with higher baseline IgE levels seem to have a better clinical response and greater compliance with dupilumab than with anti-IgE or anti-IL5/IL5R agents. These observations provide robust insights into the mechanistic aspects of AERD. Future directions might involve more studies on understanding the role of a novel eicosanoid candidate, 15-Oxo-EET, as well as of basophils, plasma cells, and macrophages in AERD. In addition, the search for laboratory diagnostic markers would be important to minimize morbidity from in-office aspirin challenges.

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Conflicts of interest

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