



# Update on the Management of Aspirin-Exacerbated Respiratory Disease

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Aspirin-exacerbated respiratory disease (AERD) is an adult-onset upper and lower airway disease consisting of eosinophilic nasal polyps, asthma, and respiratory reactions to cyclooxygenase 1 (COX-1) inhibitors. Management includes guideline-based treatment of asthma and sinus disease, avoidance of COX-1 inhibitors, and for some patients aspirin desensitization followed by high-dose aspirin therapy. Despite this, many patients have inadequately controlled symptoms and require multiple sinus surgeries. In this review, we discuss the current standard approaches to the management of AERD, and we introduce several therapeutics under development that may hold promise for the treatment of AERD.

**Key Words:** Aspirin-exacerbated respiratory disease; Samter's triad; nasal polyps; aspirin desensitization

## INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) is an acquired inflammatory disease of the upper and lower airways and is characterized by eosinophilic sinusitis with recurrent nasal polyps, asthma, and respiratory reactions to medications that inhibit cyclooxygenase 1 (COX-1). It occurs in 7% of all adult asthmatics, but is found in a disproportionately higher number of adults with severe asthma.<sup>1</sup> Onset of symptoms typically occurs in young adulthood with nasal congestion, sinus disease, and nasal polyposis, followed by development of asthma symptoms, then hypersensitivity to COX-1 inhibitors<sup>2</sup>; however, symptoms do not necessarily arise in that sequence and not all patients have prominent lower respiratory symptoms. Upon ingestion of a COX-1 inhibitor, such as aspirin or a non-steroidal anti-inflammatory drug (NSAID), patients develop upper and/or lower airway symptoms within 30-120 minutes, which often include rhinorrhea, nasal congestion, ocular pruritus and erythema, and bronchospasm.<sup>3</sup> Some patients also develop skin symptoms such as rash and flushing, or gastrointestinal symptoms such as abdominal pain, vomiting, or diarrhea.<sup>4</sup> However, systemic symptoms involving the cardiovascular system are rare. Exposure to a COX-1 inhibitor is not in itself the cause of the disease, but instead exacerbates the underlying pathobiology, resulting in an acute hypersensitivity reaction that leads to the more severe clinical manifestations. Symptoms are chronic and often progressive in nature regardless of exposure to aspirin or NSAIDs. Diagnosis is suspected when clinical

history is compatible with AERD, but aspirin challenges are required to confirm diagnosis when the patient has no history of NSAID exposure or if clinical history is uncertain.<sup>5</sup> Currently, there are no available biomarkers with sufficient sensitivity and specificity to independently confirm a diagnosis of AERD.<sup>6</sup>

Mechanisms underlying AERD are not completely understood, but are known to involve abnormal arachidonic acid metabolism with overproduction of cysteinyl leukotrienes (CysLTs)<sup>7,8</sup> and proinflammatory prostaglandins (PGs)<sup>9,10</sup> as well as underproduction of the anti-inflammatory prostaglandin PGE<sub>2</sub>.<sup>11</sup> At the tissue level, the disease is characterized by eosinophilic inflammation of the sinus and bronchial mucosa<sup>12</sup> with the presence of degranulated mast cells<sup>13</sup> and an increase in platelet-adherent leukocytes.<sup>14</sup> The pathogenesis of aspirin-induced reactions may reflect depletion of COX-1-dependent production of PGE<sub>2</sub> leading to further tissue inflammation and an acute increase in upper and lower airway symptoms.<sup>15</sup> Here, we will review the management of AERD and will discuss novel therapeutics that may target the underlying pathobiology of the disease.

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## MANAGEMENT

Standard management of AERD involves treatment of asthma and chronic rhinosinusitis (CRS) as per published guidelines<sup>16,17</sup> with the addition of leukotriene-modifying medications for all patients and aspirin/NSAID avoidance. In most cases, aspirin desensitization and initiation of high-dose daily aspirin is also beneficial.

### Aspirin desensitization

Aspirin desensitization is a safe and effective tool for the management of AERD when performed by experienced physicians. Indications for aspirin desensitization in AERD include failure of standard medical therapies, need for frequent oral corticosteroid bursts, and recurrent nasal polyps.<sup>18</sup> Aspirin desensitization can also be performed when patients with AERD require daily aspirin therapy for an alternate reason, such as coronary artery disease.<sup>19,20</sup> Desensitization may be required for patients with chronic pain requiring NSAIDs. Alternative agents, such as acetaminophen or celecoxib are generally safe, but in high doses may elicit reactions in some very sensitive AERD patients.<sup>21</sup>

Stevenson *et al.*<sup>22</sup> conducted the first randomized, placebo-controlled trial of aspirin desensitization for AERD in 1984. Following aspirin desensitization, most patients on high-dose aspirin experienced improvement in sinonasal symptoms and half of the patients experienced improvement in their asthma symptoms as well.<sup>22</sup> Subsequent observational studies confirmed that aspirin desensitization followed by high-dose aspirin therapy improves upper and lower respiratory symptoms, slows polyp regrowth, and decreases topical and oral corticosteroid use.<sup>23-26</sup> The results of a second double-blind, placebo-controlled study of aspirin desensitization and high-dose aspirin treatment in AERD were recently published. As compared to a control group of AERD patients who were treated with a placebo, the patients with AERD who were desensitized to aspirin and treated with 624 mg of daily aspirin for 6 months demonstrated improvement in sinonasal and asthma symptoms with reduction in inhaled corticosteroid use.<sup>27</sup>

Benefits of high-dose daily aspirin therapy include slowed nasal polyp regrowth and reduced need for sinus surgery,<sup>23,28</sup> improved sense of smell, decreased need for topical and oral corticosteroids, and reduced frequency of sinus infections.<sup>24</sup> Targeting patients who have required multiple endoscopic sinus surgeries for polyp removal provides significant benefits. A retrospective analysis found that over a 2-year period, no patients who were on daily aspirin required repeat polypectomies, whereas 80% of the patients not on aspirin required repeat polypectomies.<sup>23</sup> Another study with long-term follow-up after aspirin desensitization demonstrated longer surgery-free intervals, with patients on daily aspirin requiring surgery only every 10 years (instead of every 3 years off aspirin).<sup>26</sup> An economic analysis found aspirin desensitization and continued high-dose

aspirin therapy to be cost-effective in reducing the need for subsequent medical interventions, even after accounting for the up-front cost of aspirin desensitization. Aspirin desensitization in AERD patients requiring aspirin for coronary artery disease is also more cost-effective than prescribing alternative antiplatelet agents.<sup>29</sup>

The optimal dosage of aspirin following desensitization was investigated in a study of patients taking either aspirin 325 mg twice daily or 650 mg twice daily. While both doses were efficacious and occurrence of side effects was similar in both groups, some patients randomized to aspirin 325 mg twice daily had to increase the dose to aspirin 650 mg twice daily to adequately control symptoms.<sup>30</sup> Thus, high-dose aspirin therapy may need titration for adequate control of symptoms. A dose of aspirin 650 mg twice daily is a reasonable starting dose, which may be continued for an initial period of 2 months and then decreased to the lower dose of 325 mg twice daily to determine if the patient can maintain satisfactory symptom control.

A recent study described a subset of AERD patients who had difficulty tolerating aspirin desensitization due to severe extra-respiratory symptoms, including cutaneous and/or gastrointestinal symptoms. These subjects were found to have strikingly dysregulated production of prostaglandins, with dramatically increased production of PGD<sub>2</sub> during their aspirin-induced reactions.<sup>4</sup> In the authors' experience, pretreatment with oral cromolyn, a mast cell stabilizer, and zileuton, a 5-lipoxygenase inhibitor, before attempting aspirin desensitization can help these patients tolerate the desensitization procedure to allow for initiation of high-dose aspirin therapy. Decreasing the rate of dose escalation during the aspirin desensitization procedure can also be helpful in allowing these patients to tolerate the desensitization.

Although nearly all patients with AERD can be desensitized to aspirin, there is a subgroup of patients who do not symptomatically improve following aspirin desensitization. In a long-term retrospective analysis of 172 patients after aspirin desensitization, 22% of the subjects reported no improvement in symptoms, or they discontinued aspirin due to side effects.<sup>24</sup> Additionally, contraindications to aspirin, including pregnancy and a history of gastric ulcers, prevent some patients from initiating daily aspirin. Therefore, while high-dose aspirin therapy can provide excellent results, continued pursuit of more efficacious, better-tolerated targeted therapies will benefit many patients with AERD.

### Leukotriene-modifying agents

Given the overproduction of CysLTs in AERD, targeting the leukotriene pathway with either leukotriene receptor antagonists such as montelukast or 5-lipoxygenase inhibitors such as zileuton is intuitive. Several studies have evaluated the effect of montelukast on lower airway symptoms in AERD. In a double-blind placebo-controlled study of aspirin-intolerant asthmatics

on moderate-to-high dose glucocorticoids, montelukast was shown to improve lung function, reduce bronchodilator use, reduce asthma exacerbations, and improve quality of life.<sup>31</sup>

Leukotriene-receptor antagonists also modify upper airway symptoms in AERD, as montelukast has been shown to decrease nasal symptoms during lysine aspirin challenge.<sup>32</sup> In a prospective study of the effect of montelukast on nasal polyposis, 3 months of montelukast therapy improved subjects' nasal symptom scores and decreased the nasal polyp tissue eosinophilia. The improvement was most significant in patients with perennial allergies.<sup>33</sup> However, this study was limited in that no placebo was used and it did not specifically target patients with AERD.

In a recent cross-sectional survey questionnaire evaluating perceived effectiveness of therapeutic interventions by 190 AERD patients, 88% of respondents had been treated with leukotriene-receptor antagonists, whereas only 24% of respondents had been treated with a 5-lipoxygenase inhibitor. Although leukotriene-receptor antagonists were more widely prescribed for AERD, only 15% of subjects found them extremely effective, whereas 28% of subjects found zileuton to be extremely effective.<sup>34</sup> While patients report more benefit from zileuton than from leukotriene-receptor antagonists, it is less frequently prescribed in AERD. This may be in part due to concern for liver toxicity and recommended transaminase monitoring while on zileuton. Analysis of liver testing results in patients on zileuton found that ALT elevations greater than 3 times the upper limit of normal occurred in 4.2% of patients on zileuton vs 1.1% of patients on placebo. Most of the elevations occurred in the first 3 months of therapy, and only 16% of those patients were symptomatic.<sup>35</sup> In another prospective trial of controlled release zileuton for patients with asthma, ALT elevations were 3 times the upper limit of normal in 1.8% of patients taking zileuton and in 0.7% of patients on placebo, and all laboratory abnormalities resolved after stopping zileuton.<sup>36</sup> When clinically indicated, zileuton can be safely used with appropriate monitoring of transaminases and may provide additional benefit to patients with AERD. Simultaneous use of a leukotriene-receptor antagonist and a 5-lipoxygenase inhibitor in AERD has not been studied, but may provide benefit in patients who are not adequately controlled on either agent independently.

### Omalizumab

There are several case reports suggesting that omalizumab may help to improve AERD symptoms and decrease the symptoms of aspirin challenges.<sup>37,38</sup> In a proof of concept, double-blind, placebo-controlled study of allergic and nonallergic patients with nasal polyps and asthma, there was a significant decrease in the total nasal endoscopic score in the treatment group. Twelve of the 24 patients in the study had aspirin sensitivity by history.<sup>39</sup> In the recent survey questionnaire of 190 AERD patients, only 16 patients had ever been treated with

omalizumab. Of those patients, 57% found it to be somewhat or extremely effective in treating symptoms.<sup>34</sup> The mechanism by which omalizumab is effective is unclear since neither the chronic inflammatory symptoms of AERD nor the aspirin-induced reactions are IgE-mediated. Despite this, many patients with AERD have been found to have elevated baseline IgE levels.<sup>40</sup> The use of omalizumab in AERD requires further studies of both mechanism and efficacy.

### Immunotherapy

Environmental allergen immunotherapy is not recommended as the standard of care for AERD, nor has it been formally investigated as a treatment specifically for AERD. The high prevalence rates of sensitization to environmental aeroallergens in the general population are paralleled in AERD, and thus many patients with AERD have comorbid allergic rhinitis. In the previously discussed survey questionnaire, 45% of subjects had concomitant allergic rhinitis and were on allergen immunotherapy. Of subjects on immunotherapy, 62% did not find it effective,<sup>34</sup> which is a much higher treatment failure rate than is commonly expected in patients with allergic rhinitis. Given the severe sinus inflammation and nasal polyposis in AERD, the effect of immunotherapy may not be sufficient to yield improvement in sinonasal symptoms. Therefore, it may be best to prescribe allergen immunotherapy only to those AERD patients who experience clear seasonal or perennial allergic symptoms in addition to their symptoms attributable to chronic nasal polyposis.

### Investigational therapies

There are several ongoing studies of novel drugs in AERD (Table), along with many new agents that may show promise in AERD and eosinophilic nasal polyposis. Current clinical trials for AERD in the United States are investigating platelet-targeted therapies, including a P2Y<sub>12</sub>-receptor antagonist (NCT01597375) and a thromboxane-receptor (TP) antagonist (NCT02216357).

P2Y<sub>12</sub> is a G protein-coupled receptor important in platelet activation and aggregation. Thienopyridines, such as clopidogrel and prasugrel, are a class of selective P2Y<sub>12</sub> inhibitors used in acute coronary syndromes for their antiplatelet activity. They are known to decrease the development of platelet-leukocyte aggregates.<sup>41</sup> At the tissue level, there is evidence that platelet-adherent leukocytes contribute to inflammation in AERD.<sup>14</sup> Several studies in mice suggest that platelets respond to CysLTs, leading to pulmonary inflammation, which can be blunted by P2Y<sub>12</sub> antagonism.<sup>42,43</sup> The P2Y<sub>12</sub> inhibitor prasugrel is currently under investigation in a double-blind, placebo-controlled crossover study to determine if P2Y<sub>12</sub> blockade reduces the severity of aspirin reactions during aspirin challenge.

TP-receptor signaling is known to induce bronchoconstriction. In a murine model of AERD, both TP-receptor antagonism and genetic deletion of TP receptors prevented reaction to ly-

**Table.** Medications for the treatment of asthma, AERD, and/or nasal polyps

Drug	Mechanism of action	Development	Comments	Ref
Montelukast Zafirlukast	CysLTR1 antagonists	Both are FDA and EMA approved for treatment of asthma	Studies show improvement in upper and lower airway symptoms	31, 32
Zileuton	5-lipoxygenase inhibitor	FDA approved for treatment of asthma	Requires monitoring of transaminases, all cases of hepatotoxicity resolved after discontinuation of medication	34-37
Omalizumab	Binds free IgE	FDA and EMA approved	A study in patients with nasal polyps showed decrease in the total nasal endoscopic score	37-39
Prasugrel	P2Y <sub>12</sub> receptor antagonist	FDA approved for acute coronary syndrome; Phase II for AERD	Under investigation in AERD to determine if it attenuates severity of aspirin reactions	NCT01597375
Ifetroban	TP receptor antagonist	Phase II	Under investigation in AERD to determine if it attenuates severity of aspirin reactions	NCT02216357
ARRY-502 AZD1981 QAW039 OC000459	CRTH2 antagonists	Phase II	Not yet studied in AERD	
Mepolizumab	Blocks IL-5	Phase II/III	Has been studied in asthma, recently completed study in nasal polyps	52, NCT01362244
Dupilumab	Blocks IL-4R $\alpha$	Phase II	Has been studied in asthma, recently completed study in nasal polyps	NCT01920893

sine aspirin challenge,<sup>44</sup> suggesting that TP antagonism may provide therapeutic benefit in humans. Furthermore, a polymorphism of the thromboxane A2 receptor (TBXA2R) was associated with AERD in a Korean population.<sup>45</sup> Ifetroban, an oral TP-receptor antagonist, is undergoing a double-blind, randomized, placebo-controlled safety and efficacy study in patients with AERD. The primary outcome under investigation is the severity of aspirin reactions in subjects.

Several drugs in development for other immune diseases may also prove to be efficacious in AERD. Targeting the effects of PGD<sub>2</sub>, which is an inflammatory lipid known to be overproduced in AERD,<sup>10</sup> may provide therapeutic benefit. PGD<sub>2</sub> and its stable metabolites signal through the G protein-coupled receptor chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes (CRTH2) to activate and recruit eosinophils, basophils, Th2 lymphocytes, and type 2 innate lymphoid cells. A recent study showed that a urinary metabolite of PGD<sub>2</sub> was elevated at baseline in AERD patients with the most severe respiratory reactions to aspirin and further increased during their aspirin-induced reactions. PGD<sub>2</sub>, likely released by activated mast cells in the respiratory tissues, may have a role in the recruitment of CRTH2<sup>+</sup>-effector cells like eosinophils and basophils to respiratory tissues in AERD.<sup>4</sup> Several orally bioavailable CRTH2 antagonists are currently in development for asthma and allergic diseases, and may be well-suited to specifically decrease inflammation in respiratory tissues of patients with AERD.

Two cytokine-targeting drugs, mepolizumab and dupilumab,

in development for asthma, may also be of use in nasal polyposis and AERD. Mepolizumab, a humanized monoclonal antibody, which binds to free IL-5 preventing it from associating with the IL-5 receptor on eosinophils, has shown promise treating patients with eosinophilic asthma.<sup>46-51</sup> IL-5 is known to be an important factor in the survival and differentiation of eosinophils, which are the dominant cell type in the nasal polyps from patients with AERD. In a randomized, double-blind, placebo-controlled study of mepolizumab for nasal polyposis, 12 of 20 patients in the treatment group had a significant reduction in nasal polyp size as measured by improved nasal polyp score and computed tomography scans 1 month after dosing. Five of the 20 patients in the treatment group had aspirin sensitivity by history.<sup>52</sup> A multicenter, randomized, double-blind, placebo-controlled investigation of mepolizumab reducing need for surgery in nasal polyps was recently completed (NCT01362244).

Dupilumab, a fully humanized monoclonal antibody, which binds the alpha subunit of the IL-4 receptor and modulates signaling of the Th2 cytokines IL-4 and IL-13, has been investigated in several atopic diseases, including eosinophilic asthma and atopic dermatitis.<sup>53,54</sup> A recently completed phase II study of dupilumab in bilateral nasal polyps included 60 patients and assessed the endoscopic nasal polyp score in comparison to placebo (NCT01920893). The formal results of this same study are currently pending, but a preliminary press release from the sponsor reported that treatment with dupilumab resulted in statistically significant reductions in nasal polyp size, along with improvements in patient-reported symptoms of sense of smell

and nasal congestion. Dupilumab has not yet been studied specifically in AERD.

### Dietary interventions

Dietary interventions targeting the dysregulated arachidonic acid pathway are also of interest in AERD. Given the known contribution of acetylsalicylic acid (aspirin) to the pathognomonic respiratory reactions in AERD and several previously published case reports of salicylate reactions in AERD patients,<sup>55,56</sup> a low salicylic acid diet was explored as a therapeutic intervention. Sommer *et al.*<sup>57</sup> conducted a prospective crossover study examining a low salicylate diet in 10 patients with AERD. Dietary sources of salicylates, including many fruits, vegetables, herbs, spices, almonds, and several oils, were eliminated from subjects' diets for 6 weeks. Of the 10 subjects who were able to complete the study, both subjective symptom scores and blinded physician endoscopic evaluation improved while on the low salicylate diet as compared to a regular diet.<sup>57</sup> A limitation of the study is that it was not blinded to subjects, and the outcomes measured were primarily subjective symptom scores.

An ongoing dietary trial is evaluating the effect of a high omega-3, low omega-6 fatty acid diet in AERD (NCT02064738). This approach targets the proinflammatory lipids formed from the metabolism of omega-6 fatty acids, which play a role in the formation of inflammatory lipid mediators important in the pathobiology of AERD, including PGD<sub>2</sub>, TXA<sub>2</sub>, and LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>. Reducing omega-6 fatty acids in the diet may decrease the production of these inflammatory mediators derived from arachidonic acid, whereas increased dietary omega-3 fatty acids may lead to increased metabolic products of eicosapentaenoic acid, which exert less inflammatory biologic activity.<sup>58</sup> Mechanistic outcomes (decrease in urinary and serum leukotrienes) and subjective symptom scoring will be assessed.

### CONCLUSION

The medical management of AERD is multifaceted and targets a variety of the inflammatory mediators and effector cells known to be important in the disease pathogenesis. Standard therapy includes guideline-based treatment of asthma and sinus disease with the addition of medications targeting the leukotriene pathway and avoidance of all COX-1 inhibitors. Most patients with AERD will benefit from aspirin desensitization and initiation of high-dose daily aspirin therapy. Therapies targeting platelets in AERD are currently under investigation. Additionally, therapeutics specifically targeting inflammatory lipid mediators and Th2 cytokines may also prove beneficial. Therefore, many therapies in development hold promise for the treatment of AERD in the future.

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