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REVIEW

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Aspirin-exacerbated respiratory disease: A review

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Abstract

Objectives: Aspirin-exacerbated respiratory disease (AERD) is a chronic respiratory condition characterized by a triad of symptoms: asthma, chronic rhinosinusitis with nasal polyposis, and a respiratory reaction to aspirin and other cyclooxygenase-1 inhibitors, also known as nonsteroidal anti-inflammatory drugs. The objective of this review is to provide otolaryngologists with an overview of the pathophysiology, diagnosis, and treatment of this under-recognized condition.

Data sources and methods: Foundational papers on AERD were reviewed, focusing on the clinical otolaryngology and allergy/immunology literature and other high impact journals or trials.

Results: AERD results from increased production of pro-inflammatory leukotrienes and a decrease in production of anti-inflammatory prostaglandins associated with the dysregulation of multiple enzymes influencing eicosanoid metabolism. Diagnosis hinges on a high index of suspicion, careful history, and confirmatory testing for all three elements. Treatments include endoscopic sinus surgery; topical, inhaled, or oral corticosteroids; aspirin desensitization; leukotriene modifying drugs; and the new class of biologics such as dupilumab.

Conclusion: AERD is an under-recognized disease associated with substantial patient-reported morbidity. We expect rapid progress in the pathophysiological understanding of this disease and available treatments in the coming decades.

Level of evidence: 5

1 | INTRODUCTION: AN OVERVIEW OF ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Aspirin-exacerbated respiratory disease (AERD) is a chronic respiratory condition characterized by a triad of symptoms: asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and a respiratory reaction to aspirin and other cyclooxygenase (COX)-1 inhibitors, also known as nonsteroidal anti-inflammatory drugs (NSAIDs). Ingestion of aspirin typically causes a respiratory reaction to ensue in an average of 90 minutes, with involvement of the upper and/or lower respiratory tract. Historically, this triad of symptoms was known by the eponym "Samter's triad," based on Max Samter's report published in 1967.[1] Currently, it is commonly designated as AERD. In Europe, it also has been known as NSAID-exacerbated respiratory disease.[2]

AERD affects roughly 9.7% of patients with nasal polyps, 7.2% of patients with asthma, and 14.9% of patients with severe asthma, accounting for roughly 1.4 million people with the diagnosis in the United States.[3] The reported prevalence is likely an underestimate due to low awareness of the disease. The diagnosis of AERD is often

delayed, with an estimated 10-year gap between onset of symptoms and age of diagnosis.[4] It is thought that aspirin or NSAID reaction may often develop later, leading to a delay.

AERD has a significant impact on quality of life due to morbidity from asthma and CRSwNP. Extra-pulmonary symptoms, in addition to sinonasal symptoms, can include gastrointestinal upset and skin symptoms, such as urticaria. Patients may also report respiratory symptoms, including nasal congestion, with alcohol ingestion.[5] Patients often have severe sinus disease that is challenging to treat medically or surgically. Given the substantial morbidity, there has been a recent surge in attention to the recognition and treatment of AERD. Novel options for medical therapy, including biologic agents, are also leading to new opportunities in the management of this condition. The aim of this article is to review the underlying pathophysiology, diagnosis, and treatment of this disease.

2 | PATHOPHYSIOLOGY

The pathogenesis of AERD involves an increase in production of pro-inflammatory leukotrienes and a decrease in production of anti-inflammatory prostaglandins. Arachidonic acid is normally broken down into prostaglandins, a process mediated by the COX pathway and inhibited by ingestion of NSAIDS. However, in AERD patients, arachidonic acid is diverted to production of cysteinyl leukotrienes (CysLTs) via the 5-lipoxygenase (5-LO) pathway (Figure 1).

CysLTs are inflammatory lipid mediators that are commonly upregulated in the pathogenesis of AERD, causing bronchoconstriction, vascular leak, mucous secretion, and increased eosinophilic inflammation. Patients with AERD have high baseline levels of CysLTs compared to healthy patients, which increase even further upon ingestion of aspirin.[6] Leukotriene production is increased in nasal polyp tissue, and levels of CysLTs increase with the severity of disease in AERD patients compared to patients with non-AERD CRSwNP.[7] LTE_4, the stable end-metabolite of arachidonic acid oxidation by CysLTs, induces the recruitment of eosinophils to the respiratory tissues and is directly associated with the magnitude of bronchoconstriction during NSAID ingestion.[8,9]

AERD patients have higher baseline levels of prostaglandin D2 (PGD2), another inflammatory lipid mediator, which increase even after ingesting aspirin. Interestingly, patients who were found to have the highest levels of PGD2 during aspirin-induced reactions also had the most severe extra-respiratory symptoms.[10] The mechanism by which PGD2 likely causes the inflammatory reaction is through its metabolite, 9a,11b-PGF2, a bronchoconstrictor, as well as through its attraction of eosinophils, basophils, and innate lymphoid type 2 cells out of the bloodstream and into respiratory tissue.[11] Interestingly, ingestion of selective COX-2 inhibitors does not induce respiratory

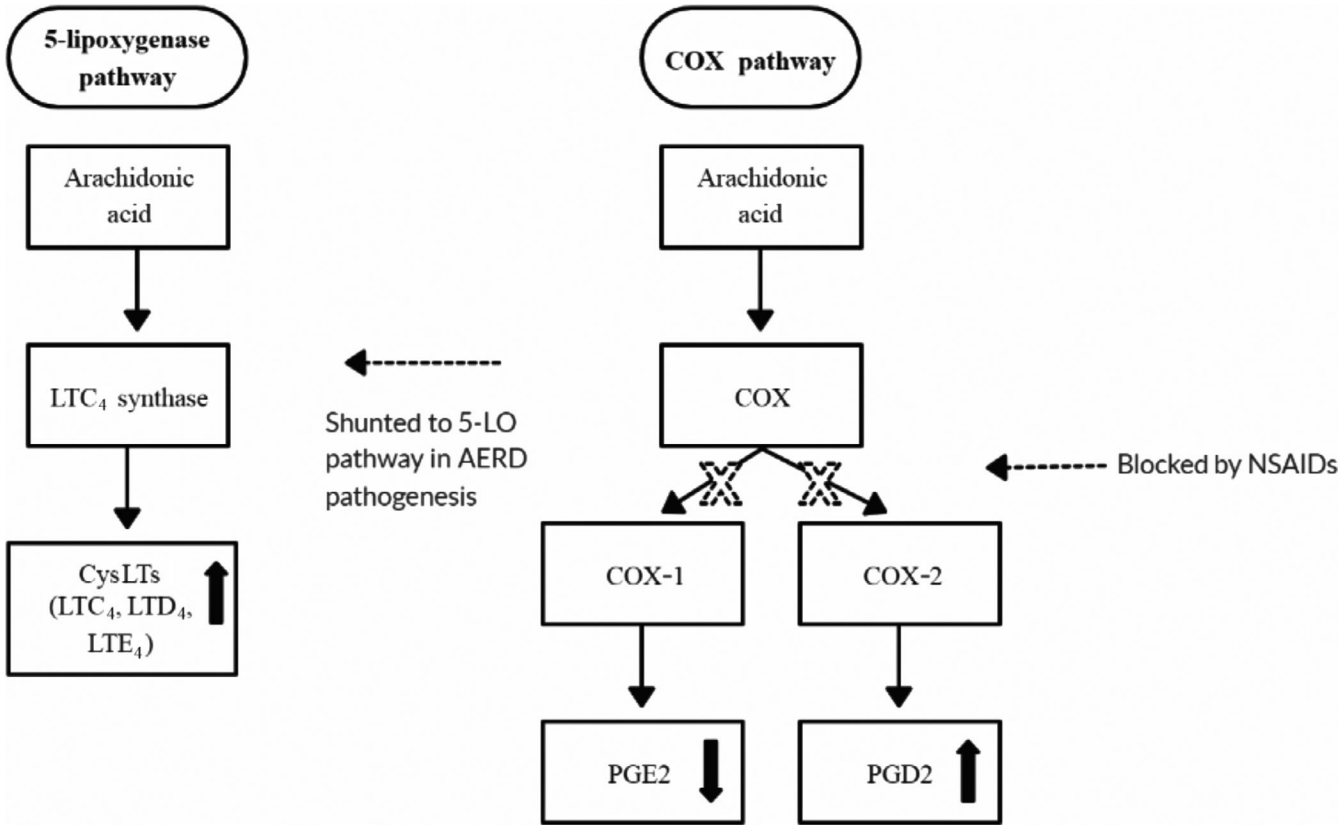

FIGURE 1 Pathogenesis of aspirin-exacerbated respiratory disease (AERD). In normal patients, arachidonic acid is broken down into cyclooxygenase (COX)-1 and COX-2, which are inhibited by nonsteroidal anti-inflammatory drugs (NSAIDS). However in AERD patients, this pathway is shunted towards the 5-lipoxygenase (5-LO) pathway, causing an increase in production of inflammatory CysLTs

reactions in patients with AERD, and could be an alternative option for pain treatment for these patients.[12] However, selective COX-2 inhibitors can only be obtained with a prescription, and thus many patients are unaware of their availability.[13]

Other key players in the pathogenesis of AERD are prostaglandin E2 (PGE2), interleukin-33 (IL-33), and thymic stromal lymphopoietin (TSLP). PGE2 regularly acts as a "check point" against 5-5-LO activity and mast cell activation. AERD patients, however, have a deficiency in PGE2 which impairs the cells' anti-inflammatory ability. Production of PGE2 in AERD patients likely depends disproportionately on COX-1, and therefore is even more depleted upon NSAID ingestion.[8] IL-33 and TSLP are cytokines that are overly expressed in nasal polyp tissue of AERD patients. Blocking IL-33 and TSLP prevents aspirin-induced changes in lung function as well as the release of mast-cell mediators. One theory is that mast cells send responses from the upstream IL-33 and TSLP to downstream effector cells, likely through mediators such as PGD2.[6]

Increases in urinary LTE_4 upon ingestion of NSAIDs are also associated with increases in the products activated by mast cells (histamine, tryptase, and PGD2). These findings indicate mast cell involvement in the upregulation of CysLTs when COX-1 is inhibited. Additionally, there is growing evidence of the role of platelets in AERD. Platelets may adhere to neutrophils, monocytes, and eosinophils which are enriched in the sinonasal tissues of AERD patients. Platelets express LTC_4 synthase, contributing to CysLT production.[6] Therefore, the dysregulation of the 5-LO pathway is achieved through multiple cell types, leading to multiple potential targets for pharmacotherapy.

3 | CLINICAL PRESENTATION

AERD presents during late childhood to adulthood, with the median age of onset around 34 years of age.[14] The disease often develops gradually, with nasal congestion and rhinorrhea usually being the first symptoms to develop. Hyposmia tends to develop later and signifies the likely development of CRSwNP. Common sinonasal symptoms in AERD patients include nasal congestion or obstruction, anosmia, and postnasal drip. Patients with AERD are often noted to have rapid nasal polyp recurrence after endoscopic sinus surgery (ESS).[14] Along with patient symptomatology, the presence of nasal polyposis or pansinus opacification with radiologic imaging should also warrant investigation for AERD.[15] Asthma tends to develop on average 2 years after initial upper respiratory tract symptoms, and aspirin-intolerance typically develops 4 years later.[16] Symptoms with aspirin ingestion include cough, wheezing, chest pain, eye watering and/or redness, flushing, rash, nausea, angioedema, and abdominal cramping.[17] A diagnosis of AERD can often be made clinically when all or some of these are present.

Because many patients tolerated NSAIDs in the past without issue, the NSAID reaction may not be recognized and patients may continue to ingest NSAIDs.[4] This is partially responsible for the large gap between onset of symptoms and the ultimate diagnosis of AERD. It is important to ask whether patients have had any type of reaction or intolerance to NSAID or aspirin, such as respiratory, gastrointestinal, and sinonasal symptoms. Some patients diagnosed with nasal polyposis and asthma previously have been warned not to take NSAIDs or aspirin, and therefore have no knowledge of their tolerance. Therefore, patients should also be asked about avoidance. Other patients have not taken NSAIDs and therefore would not be aware of a reaction. Simply asking "do you have an allergy to NSAIDs" is not sufficient to assess for the diagnosis of AERD because of these subtleties in presentation.

A recent study found that more than 70% of AERD patients reported that the diagnosis had at least a moderate negative effect on their quality of life. Main contributors to diminished quality of life are anosmia and otologic symptoms. Chronic otitis media, hearing loss, and eustachian tube dysfunction are understudied but common in AERD patients, with a high comorbidity of middle ear infections requiring antibiotics (41.5%), middle ear effusion (30%), vertigo (22.1%), and chronic ear drainage (6.1%).[18] Although an underrecognized burden of disease, the otologic symptoms reported by AERD patients cause a significantly high emotional and social handicap, and should prompt treating physicians to conduct otologic evaluation.[18] Interestingly, anosmia has been described as the top symptom that leads to diminished quality of life in patients with AERD.[19]

4 | DIAGNOSIS

Generally, the diagnosis of CRSwNP by an otolaryngologist and the diagnosis of asthma by a primary care physician or specialist are relatively uncomplicated. Nasal polyps can be confirmed with anterior rhinoscopy if significant or by sinonasal endoscopy for less severe cases. If asthma and nasal polyposis have been confirmed, then aspirin or NSAID allergy confirmation is necessary to achieve a diagnosis of AERD. If a patient presents with a history of more than one episode of reaction to aspirin or other NSAIDS, then a diagnosis of AERD can be made with some degree of certainty. However, if they have no history of aspirin or NSAID use or it is ambiguous, then proper diagnosis of AERD would require a physician-observed aspirin challenge, where responses are measured by clinical presentation and pulmonary function tests.[20] In established allergy centers with experienced providers and staff, oral challenges can be done safely in the outpatient setting. An inpatient setting should be considered if a patient is receiving beta-blockers, had a recent myocardial infarction, and/or has severe asthma.[21]

Aspirin challenge testing starts with a low dose of aspirin, and gradually increasing dosages are given until a positive response is achieved. The typical provoking dose is in the range of 30 to 150 mg, with an average of 60 to 75 mg.[15] Typically, doses start at 20 to 40 mg, with most symptoms occurring between 45 and 100 mg within 30 to 60 minutes of ingestion of the provoking dose. Doses increase incrementally with 3 hours or less between each dose. No additional reactions are found to occur at 650 mg and greater.[22] Once a

respiratory reaction is observed, the diagnosis of AERD can then be confirmed. The dose range is due partly to differences in the typical aspirin dose available in different countries.

Aspirin challenge testing can now routinely be completed in 1 day, lasting approximately 9 hours. The timing sequence for a typical aspirin challenge was determined by DeGregorio et al at the Brigham and Women's Hospital AERD center.[23] At our center, we start at a dose of 40.5 mg and give a dose every 90 minutes, with patient reported outcome measures and pulmonary function tests as well as vital signs taken prior to the next dose, until a reaction is observed, or until a 325 mg dose is achieved. Clinicians can also utilize leukotriene-modifying drugs as during aspirin challenge protocols to limit the severity of the respiratory reaction provoked. When pretreated with montelukast and zileuton, AERD patients had a 10% to 20% increase in FEV-1, less severe asthma attacks, and a decrease in lower respiratory tract symptoms.[24,25]

Pulmonary function tests are used to document the respiratory response, especially if it is not evident on observation or physical examination. Forced expiratory volume in 1 second (FEV-1) is measured every 30 minutes up to 120 minutes after the final dosage is given. A positive reaction is defined as a decrease in FEV-1 greater than 20%.[26] If no response is achieved regardless of the dose, then the patient does not have aspirin sensitivity.

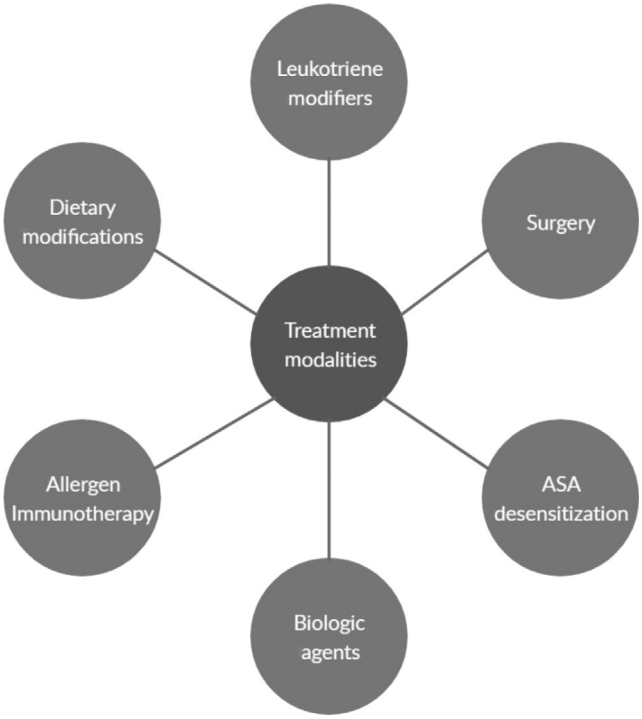

FIGURE 2 Treatment modalities. Treatment options for patients with aspirin-exacerbated respiratory disease work best when used in combination and should be tailored to the patient

5 | TREATMENT

5.1 | Endoscopic sinus surgery

Many patients will have severe CRSwNP by the time they present for treatment.[13] Although ESS can provide symptomatic relief for most patients, recurrence of nasal polyposis is often rapid in the absence of postoperative medical management. ESS for AERD patients involves removing the nasal polyps, widening the ostia of the paranasal sinuses. This allows improved delivery of topical medications, including nasal steroids. In addition, treatments such as aspirin desensitization and leukotriene modifiers can be added postoperatively (Figure 2). After ESS, patients show a decrease in urinary LTE_4 and higher PGE2 levels, and have less severe reactions to aspirin desensitization.[27] ESS without any additional therapies for AERD patients causes an initial improvement in symptoms, but has a high rate of recurrence.[28] Therefore, the greatest impact of ESS in patients with AERD is when surgery is combined with postoperative aspirin desensitization, topical corticosteroids or biologics.

The Draf III procedure, also known as the endoscopic modified Lothrop procedure or bilateral frontal sinus drill-out, can be considered as an adjunct surgical procedure to treat recurrent frontal sinus symptoms or disease in patients with AERD if routine ESS fails. AERD patients have been shown to be at higher risk of failure of traditional ESS without Draf III.[29] The Draf III procedure involves removing the bilateral medial frontal sinus floor extending from lamina papyracea to contralateral lamina papyracea, and resecting the superior nasal septum, frontal intersinus septum, and other frontal sinus partitions.[30] This creates a common drainage pathway for the bilateral frontal sinuses, leading to improved distribution of topical sinus rinses.[31] In a population of CRS patients with or without AERD, the Draf III procedure was found to improve symptoms in 82% of patients, with improvement in 76% of patients when used as a salvage surgery after failed ESS.[32] Within this cohort, AERD was associated with an even greater likelihood of improvement vs non-AERD patients. In a cohort of 31 AERD patients with prospectively collected data who underwent Draf III, 18 (58%) of patients experienced polyp recurrence and 7 (28%) underwent revision Draf III at a mean of 45 months postoperatively.[33] When compared with non-AERD patients undergoing Draf III, AERD patients were at higher risk of polyp recurrence. Recently there has been debate as to whether this procedure should be considered as an early option for AERD patients who are undergoing primary ESS, and no randomized data to address this question. Because the biological agents are new, currently published surgical studies reflect long-term outcomes without the benefit of all currently available treatments. Current areas of investigation include the timing, extent, and long-term outcomes of surgery within the context of new treatments.

Surgery needs to be synchronized with other postoperative treatments, and a multidisciplinary approach with otolaryngologists and allergists should be considered. If patients are already on aspirin preoperatively, a plan regarding aspirin cessation with repeat desensitization after ESS or continuation of therapy around the time of ESS needs to be fully discussed and coordinated. Aspirin desensitization has optimal effects when done roughly 2 to 4 weeks

postoperatively.[21] Aspirin desensitization is thought to be safer when completed postoperatively, due to the reduction of leukotriene-containing polyp tissue burden.

5.2 | Corticosteroids

Corticosteroids can be used in different forms to treat AERD:

1. intranasal sprays or irrigations for treatment of CRSwNP,
2. inhaled steroids for asthma control,
3. oral steroids to help asthma and/or sinonasal symptoms.

Fluticasone propionate and other intranasal corticosteroids decrease the number of eosinophils and mast cells in sinonasal mucosa. This leads to a decrease in inflammation, specifically with improvement in nasal congestion symptoms.[34] The addition of budesonide inhalant suspension to nasal saline irrigations can also improve the sense of smell and decrease nasal polyps as evidenced by CT scans. Limited side effects with the use of topical steroids, results in frequent use, but frequently they are insufficient to control AERD symptoms without other concurrent therapy.[35] Treatment with topical intranasal corticosteroids, whether in spray or irrigation form, may be utilized after ESS as well to try to slow polyp regrowth.

Oral systemic corticosteroids can provide rapid relief of nasal and respiratory symptoms. Unfortunately, long-term use can result in significant side effects, including endocrine, musculoskeletal, and neurological morbidity.[36] Therefore, oral corticosteroids are most frequently used in a short burst or taper format.

Inhaled corticosteroids have been used for many years to treat aspirin-tolerant asthma, and have also been helpful in the treatment of AERD. However, even high doses of inhaled corticosteroids may not be sufficient to control the asthmatic portion of AERD, and work better when combined with leukotriene modifying drugs.[37]

5.3 | Aspirin desensitization

Aspirin desensitization and daily aspirin therapy is currently an option for treatment for patients with AERD. It results in slowed nasal polyp regrowth after ESS, longer surgery-free intervals, improved sense of smell, and a decreased need for corticosteroids.[17] A recent meta-analysis of benefits and harms from aspirin desensitization treatment concluded that there was improvement in quality of life, including improvement in respiratory symptoms and mean SNOT-22 score improvement of 10.27 (95% confidence interval [CI], −6.39 to −14.15).[38] Of note, the mean but not the 95% CI SNOT-22 score exceeded the minimum clinically important difference of 9.0.[39] An increase in complications relative to placebo sufficient to warrant drug discontinuation was also encountered, such as asthma exacerbation, gastritis, and bleeding events.[38] The mechanism for aspirin desensitization is still not fully understood. One study found that high-dose aspirin therapy paradoxically increased markers of type 2 inflammation in patients with AERD, despite the fact that it reduced nasal symptoms.[40]

Aspirin desensitization, like an aspirin challenge, can be completed in an outpatient setting in one full day, as demonstrated by DeGregorio et al.[23] It is critical that aspirin desensitization is conducted under supervision of a physician who is properly trained and in a well-equipped clinic as severe reactions can occur. Desensitization begins by starting the patient at 40.5 mg of aspirin and observing for any respiratory reaction. This is continued until 325 mg is achieved.[23] With each increase in dosage, the respiratory reactions will become milder and shorter, and once 325 mg is achieved any dosage over that will generally not induce a reaction. Aspirin must then be taken daily in perpetuity, and a loss of desensitization will ensue if discontinued for over 48 hours.[13,41] The specific doses are often slightly different in different countries based on the typically available aspirin dose.[38,42,43] For example, in some European countries, doses of 50, 100, or 100 mg multiples (ie, up to 800 mg) may be used during desensitization or treatment.[42]

5.4 | Leukotriene-modifying drugs

The use of leukotriene receptor antagonists and 5-lipooxygenase inhibitors can be useful in the treatment of AERD due to decreased production of CysLTs. Montelukast, a commonly used selective leukotriene receptor antagonist, has been shown to improve FEV-1 by 10.2% on average, and peak expiratory flow rate difference of 25.5 F/min. It also causes significant decreases in the number of asthma symptoms experienced throughout the day, as well as improved scores on asthma-specific quality-of-life measurements.[37]

Zileuton, a leukotriene-inhibitor, inhibits 5-LO and therefore blocks downstream formation of CysLTs, including LTE_4.[44] Improvements of over 20% in FEV-1 scores are seen within hours, as well as higher peak expiratory flow rates, diminished nasal dysfunction, return of smell, and inhibited aspirin-induced bronchoconstriction.[44] Zileuton has been found to be more effective than montelukast in treating asthma symptoms due its upstream inhibition of 5-LO resulting in downregulation of all downstream CysLTs, whereas montelukast and other LT1 receptor antagonists do not significantly affect LTE_4.[13] There is potential, self-limited hepatic damage associated with Zileuton and therefore patients should be monitored during treatment.[45]

5.5 | Biologic agents

Biologic agents are often employed to control respiratory disease in patients with asthma, and therefore have been used in patients with AERD. Mepolizumab is a humanized monoclonal antibody that blocks IL-5 leading to improved nasal symptoms and lung function in severe eosinophilic asthma patients with CRS.[46] Mepolizumab was found to continuously reduce eosinophil count over the course of a 40-week trial for patients with severe eosinophilic asthma, with a clinically significant decreased rate of asthma exacerbations (1.74 in placebo group and 0.83 in subcutaneous mepolizumab group) as well as a decreased rate of hospitalizations due to exacerbations.[47] Therefore, mepolizumab is an effective treatment for upper and lower airway respiratory symptoms in AERD patients with eosinophilic asthma.

Other biologic agents include omalizumab and dupilumab. Omalizumab is a monoclonal IgE antibody that binds to free IgE, leading to a decrease of IgE binding to mast cells and basophils. In a study of 21 patients, omalizumab caused a 76.2% decrease in LTE_4 urinary concentration, and an 89.0% decrease in urinary concentration of PGF2. Improvement for asthma and/or sinonasal symptoms was seen within the first week in 52.4% of patients, and within 3 months for 18 of 21 patients (n = 3 nonresponders).[48]

Dupilumab is a monoclonal antibody that binds to the shared receptor for IL-4 and IL-13, thus inhibiting both IL-4 and IL-13. It was originally FDA approved for use in atopic dermatitis, and then approved for treatment of moderate to severe asthma with an eosinophilic phenotype or dependent on steroids. It recently became the first biologic therapy approved for the treatment of CRSwNP and has been found to significantly improve FEV-1, Lund-Mackay, and SNOT-22 scores, as well as patient-reported and objective measures of sense of smell.[49]

5.6 | Dietary modifications

Dietary modifications have also been reported to improve symptoms in patients with AERD. Laidlaw et al at Brigham and Women's Hospital AERD Center found that a 2-week diet high in omega-3 fatty acids and low in omega-6 fatty acids reduced leukotriene production, ultimately decreasing inflammation.[50] Reduction in alcohol intake is another nonmedical way to reduce AERD symptoms. Ingestion of any amount of alcohol was found to induce nasal and/or bronchial symptoms in roughly 75% of patients.[5] Therefore, AERD patients may benefit from cutting out all alcoholic beverages from their diet.

5.7 | Allergen immunotherapy

In a study conducted by White and Ta, more than half of AERD patients on allergen immunotherapy for concomitant allergies found the treatment to be ineffective for their AERD symptoms, and only 8% found it to be extremely effective.[51] This suggests that the symptoms related to other environmental allergies are not responsible for the majority of symptoms in AERD and therefore standard allergen immunotherapy will be ineffective for many AERD patients. This is important for clinicians treating AERD to consider, and therefore recognize that patients with AERD might not notice improvement with allergen immunotherapy alone if their primary symptoms are not related to environmental allergies and rather require more intensive treatment for AERD with other therapies.[17]

5.8 | Current areas of investigation and drugs in trial phase

While we have come a long way in understanding and treating AERD, there are still gaps in awareness of the disease, pathophysiology, and treatment options. Investigations of new drugs will hopefully bring increased understanding of AERD. Multiple new pharmacologic agents are currently in clinical trials, including those targeting the role of platelets in the disease.[52] Clinical trials are currently underway to determine the safety and efficacy of ifetroban, a thromboxane receptor antagonist.[52] Prasugrel, another antiplatelet drug, blocks transcellular CysLT synthesis and has been approved for acute coronary syndrome. It is currently under investigation for AERD to determine its ability to reduce the severity of respiratory reactions during aspirin challenges.[17] Investigations of these drugs will hopefully enable researchers to better understand the role of platelets in the pathogenesis of AERD.

Future studies will also need to address the long-term outcomes and optimal multimodality regimens for patients. For example, the potential combination, extent and timing of surgery, aspirin desensitization, the biologic agents, and other treatments are not established and are currently being investigated. There are no data comparing patients with and without aspirin desensitization after full ESS vs Draf III, and likewise no randomized data on long term patient outcomes when surgery is combined with the biologic agents. These areas require further investigation.

6 | CONCLUSION

AERD is an under-diagnosed medical condition with significant morbidity causing pulmonary, sinonasal and systemic symptoms. Diagnosis often requires confirmatory testing, including otolaryngology evaluation for sinonasal polyposis, pulmonary testing for asthma, and aspirin challenge testing. Patients benefit from a multidisciplinary approach to diagnosis and treatment. Our understanding of the pathophysiology of AERD is rapidly evolving and there have been many advancements in the treatment of this disease. Further research is still needed to understand the disease mechanism, develop drug targets, and explore the optimal timing and extent of ESS to improve outcomes in the context of new treatments.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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