

Review

Aspirin-exacerbated respiratory disease

Updates in the era of biologics

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Key Messages

- Aspirin-exacerbated respiratory disease (AERD) is characterized by difficult-to-treat chronic upper and lower airway inflammation, with many patients failing first-line, standard-of-care treatment.
- AERD is characterized by type 2 inflammation and overproduction of cysteinyl leukotrienes and inflammatory prostaglandins.
- Treatment of AERD includes standard-of-care treatment for asthma and chronic rhinosinusitis with nasal polyps, leukotriene modification, aspirin desensitization followed by daily aspirin therapy, and respiratory biologic therapy for asthma and chronic rhinosinusitis with nasal polyps.
- Future studies focused on responder analyses for respiratory biologics and aspirin therapy after desensitization will allow for optimization of personalized treatment for patients with AERD.

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ABSTRACT

Objective: Aspirin-exacerbated respiratory disease (AERD) is a chronic respiratory condition characterized by severe chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic asthma, and respiratory reactions to cyclooxygenase inhibitors. The management of AERD has evolved recently with the availability of respiratory biologics for treatment of severe asthma and CRSwNP. The objective of this review is to provide an update on the management of AERD in the era of respiratory biologic therapy.

Data Sources: A literature review of pathogenesis and treatment of AERD, with a specific focus on biologic therapies in AERD, was performed through publications gathered from PubMed.

Study Selections: Original research, randomized controlled trials, retrospective studies, meta-analyses, and case series of high relevance are selected and reviewed.

Results: Aspirin therapy after desensitization (ATAD) and respiratory biologic therapies targeting interleukin (IL)-4Rα, IL-5, IL-5Rα, and immunoglobulin E, all have some efficacy in the treatment of CRSwNP and asthma in patients with AERD. There are currently no head-to-head studies comparing ATAD vs respiratory biologic therapy, or specific respiratory biologics, for asthma and CRSwNP in patients with AERD.

Conclusion: Advances in our understanding of the fundamental drivers of the chronic respiratory inflammation in asthma and CRSwNP have led to the identification of several potential therapeutic targets for these diseases that can be used in patients with AERD. Further study of the use of ATAD and biologic therapy, independently and together, will help to inform future treatment algorithms for patients with AERD.

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Introduction

Aspirin-exacerbated respiratory disease (AERD), also referred to as Samter's triad, nonsteroidal anti-inflammatory drug (NSAID)

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—exacerbated respiratory disease, and aspirin-sensitive asthma, is characterized by adult-onset asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and hypersensitivity reactions to all cyclooxygenase (COX) 1 inhibitors.¹ Management of CRSwNP and asthma can be challenging in patients with AERD, with many patient failing first-line therapies.² However, advances in our understanding of the mechanisms underlying the chronic respiratory tract inflammation

in CRSwNP and AERD have led to novel treatments for patients with AERD, including respiratory biologic therapy. We will describe the clinical presentation of AERD, discuss updates in our understanding of the mechanisms of AERD, and review updates in treatment options for patients with AERD with a specific focus on biologic therapy.

Clinical Presentation and Diagnosis of Aspirin-Exacerbated Respiratory Disease

Classically, AERD presents with the triad of adult-onset asthma, severe eosinophilic CRSwNP, and upper and lower respiratory reactions to aspirin and NSAIDs. In a large systematic review, AERD was found to occur in approximately 7% of adults with asthma, but the prevalence was twice as high in adults with severe asthma.³ AERD is usually an adult-onset disease with the average onset of occurring in the fourth decade of life,^{4,5} but rare pediatric cases have been described.^{6,7} In a retrospective review comparing patients with AERD, CRSwNP without comorbid asthma, and CRSwNP with asthma, the patients with AERD were younger at the time of first sinus surgery compared with patients with aspirin-tolerant CRSwNP with and without asthma.⁵

Patients with AERD have severe and often difficult-to-treat CRSwNP leading to chronic nasal congestion, hyposmia or anosmia, rhinorrhea, and postnasal drip. After endoscopic sinus surgery (ESS), the risk of nasal polyp recurrence is higher in patients with AERD compared with patients with aspirin-tolerant CRSwNP, and nasal polyp recurrence will occur in most patients without intensive adjuvant interventions.^{8,9} Furthermore, patients with AERD are likely to require more revision ESSs and chronic oral steroid use compared with aspirin-tolerant patients with CRSwNP.⁵

Pathognomonic respiratory reactions to COX-1 inhibitors occur in patients with AERD and manifest as upper and lower respiratory symptoms, including rhinorrhea, nasal congestion, ocular erythema, and bronchospasm.¹ Symptoms do not occur immediately after NSAID ingestion; the average time between ingestion of aspirin and onset of symptoms is approximately 45 to 60 minutes during physician-observed, graded-dose challenges depending on the specific aspirin preparation used, with more than 95% of patients with AERD reacting at doses of 162 mg of aspirin or less.^{10,11} In addition to COX-1 inhibitor-elicited upper and lower respiratory tract symptoms, some patients with AERD develop extrarespiratory symptoms including cutaneous symptoms (flushing, pruritic rash) and gastrointestinal symptoms (abdominal pain, nausea, vomiting, pancreatitis).^{12,13} Another common symptom reported by patients with AERD is upper and lower respiratory symptoms after ingestion of alcohol. Although this symptom is not isolated to patients with AERD, it is more common in patients with AERD than in patients with aspirin-tolerant asthma or CRSwNP.^{14,15}

The diagnosis of AERD can be made on the basis of clinical criteria in a patient with compatible clinical history of CRSwNP, asthma, and history of respiratory reactions to aspirin or NSAIDs. However, in instances of diagnostic uncertainty, physician-observed graded-dose aspirin challenges are standard for diagnosis of AERD.¹⁶ The timing of diagnostic aspirin/NSAID challenges for AERD is important; if challenges are done after a sinus surgery with debulking of nasal polyp tissue, patients may not exhibit the typical upper and lower respiratory symptoms, and the diagnosis could be missed.^{17,18} At this time, there are no readily available diagnostic biomarkers with adequate sensitivity or specificity to identify patients with AERD.¹⁹

Mechanisms of Aspirin-Exacerbated Respiratory Disease

Our understanding of mechanisms underlying AERD continues to improve, with novel insights arising from clinical trials of various therapeutic drugs, mouse models, and dedicated human tissue studies using advanced cellular and molecular technologies, as discussed in several recent mechanistic reviews.^{20–22} AERD is characterized by

type 2 inflammation and overproduction of cysteinyl leukotrienes and inflammatory prostaglandins (Fig 1).^{1,23,24} Nasal polyp tissue from patients with AERD is marked by dense tissue eosinophilia, activated mast cells, ILC2s, platelet-adherent leukocytes, basophils, antibody-secreting cells, and local antibody production.^{23,25–32} There is also a role for the innate type 2 cytokines thymic stromal lymphopoietin and interleukin (IL)-33 in propagating mast cell activation in patients with AERD.^{33–35} Patients with AERD have elevated nasal polyp tissue immunoglobulin (Ig)E levels^{28,36} compared with those with aspirin-tolerant CRSwNP. Higher nasal polyp tissue IgE levels correlate with more severe sinonasal disease in patients with AERD.²⁸ Recently, inflammatory heterogeneity within the classic type 2 AERD phenotype has been described,³⁷ and patients with AERD and high type 1 or type 3 inflammatory markers had the highest likelihood of recurrence after ESS.³⁸

Patients with AERD have overproduction of cysteinyl leukotrienes (cysLTs) and inflammatory prostaglandins (PGs)^{39,40} and underproduction of the anti-inflammatory prostaglandin PGE₂.⁴¹ Both cysLTs and inflammatory prostaglandins likely play a role in amplifying respiratory tract inflammation and eosinophilia.⁴² Cysteinyl leukotrienes^{43,44} and inflammatory prostaglandins^{12,33} both surge during the COX-1 inhibitor-induced reactions, mediating bronchoconstriction and acute respiratory symptoms characteristic of COX-1 inhibitor-induced reactions. The pathogenesis of COX-1 inhibitor-induced reactions in AERD may be due in part to depletion of COX-1–dependent PGE₂, leading to further respiratory tissue inflammation.⁴⁵

Management of Aspirin-Exacerbated Respiratory Disease

Aspirin Desensitization

Aspirin therapy after desensitization (ATAD) has long been a cornerstone of therapy in AERD.^{46,47} During aspirin desensitization, sequentially higher doses of aspirin are administered until the patient develops a state of tolerance with a typical target dose of aspirin 325 mg daily to 650 mg by mouth twice daily.^{48,49} The precise mechanism of this seemingly paradoxical therapy is not yet fully defined. Interestingly, aspirin desensitization seems to actually increase levels of type 2 inflammatory biomarkers, including cysLTs.⁵⁰ It has been hypothesized that the increase in cysLTs induced by aspirin desensitization may ultimately decrease mast cell-derived PGD₂, a potent proinflammatory mediator in AERD.⁵¹

The efficacy of ATAD in the treatment of AERD has been confirmed in multiple studies, including double-blind, placebo-controlled trials and smaller observational studies. For the treatment of sinus disease, ATAD significantly improves nasal symptoms and sinonasal outcome test (SNOT)-20 scores,^{46,52} lessens the need for intranasal and systemic corticosteroids,^{46,53,54} and mitigates the rate of nasal polyp relapse after sinus surgery.^{53,55} In the treatment of asthma, ATAD improves asthma control questionnaire (ACQ) scores,⁵⁶ significantly increases forced expiratory volume in 1 second (FEV₁),⁵⁷ and leads to reductions in dosages of inhaled corticosteroids.⁵² ATAD also improves health-related quality of life, leading to a significant reduction in symptoms and clinical complaints related to AERD.^{55,58,59} ATAD provides cross-desensitization to other NSAIDs, should they be required for cardiac or analgesic treatment.⁶⁰

The vast majority of patients find ATAD effective, with a long-term retrospective study revealing that 85% of patients who took ATAD for 10 years reporting it to be helpful for their AERD symptoms.⁵⁹ Another survey-based study of 98 patients with AERD, assessing treatment response, revealed that 75% of patients who took ATAD found it to be effective.²

Yet, despite the numerous and established clinical benefits of ATAD, not all patients are offered this therapy. A 2016 survey of allergists indicated that nearly 40% do not offer aspirin desensitization,

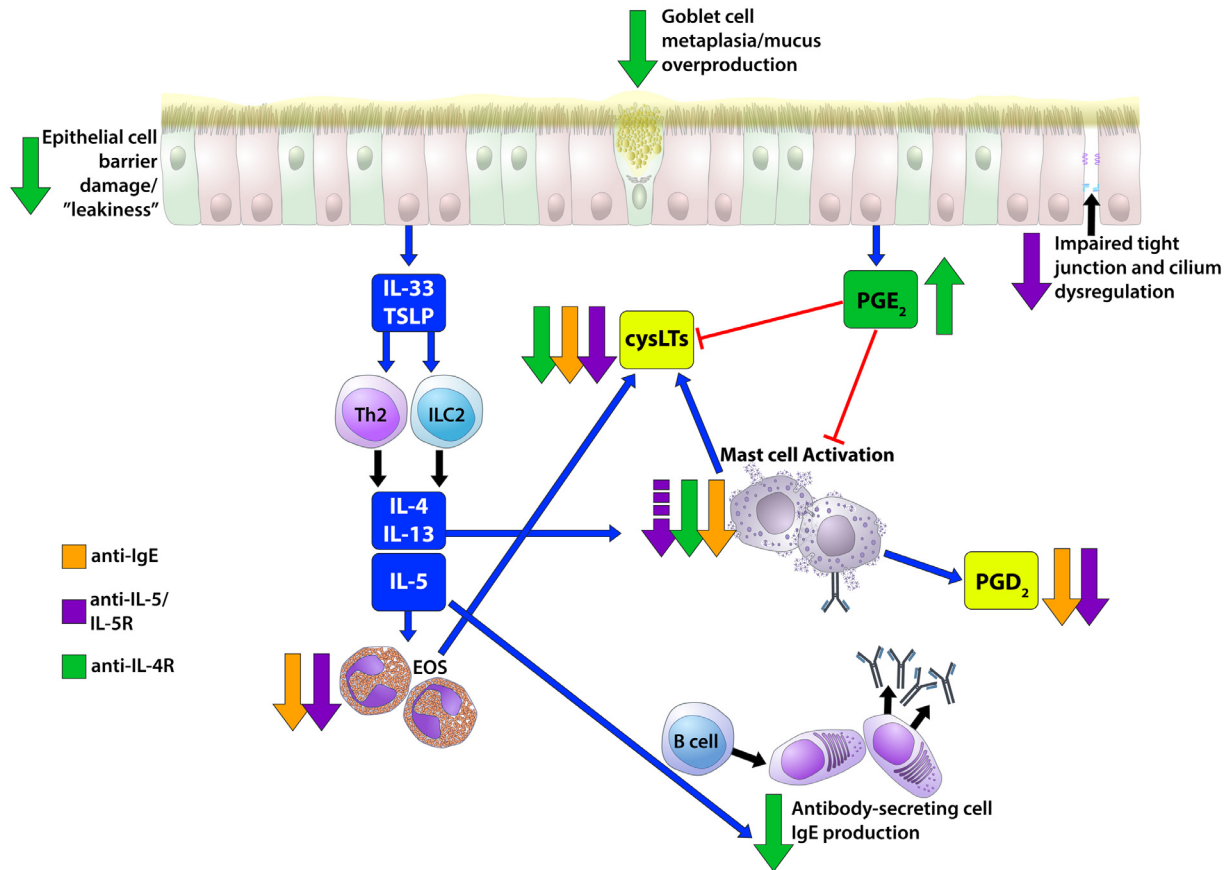


Figure 1. Specific mechanisms of omalizumab, mepolizumab, and dupilumab in patients with AERD. Solid colored arrows (orange for anti-IgE, purple for anti-IL-5, and green for anti-IL-4R) highlight known mechanistic impacts of specific biologic agents in AERD. The dashed purple arrow highlights a possible impact of anti-IL-5 treatment in AERD. AERD, aspirin-exacerbated respiratory disease; EOS, eosinophils; IgE, immunoglobulin E; IL-5, interleukin-5; IL-4R, interleukin-4 receptor.

partly because of logistical issues in arranging the procedure, safety concerns, and lack of exposure during training.⁶¹ In the years following that report, the availability of aspirin desensitization was increased, with most eligible patients able to access the procedure.⁶²

Although many patients derive a significant benefit from ATAD, there are patients who either find no improvement at all or find inadequate symptomatic relief.^{2,54} Moreover, some patients are unable to tolerate ATAD, related to adverse effects of high-dose aspirin, including bruising, major bleeding, gastritis, worsened respiratory symptoms, and rash.^{63–65} Gastrointestinal adverse effects are the most common reason for discontinuation, with approximately 50% of patients on ATAD reporting this adverse effect; this seems to occur at a similar rate at either a 325 mg or a 650 mg twice-daily dose.⁴⁸ Furthermore, risk of bleeding must be seriously considered before initiation of ATAD given known increased risks even with low doses of aspirin.⁶⁶ Although aspirin desensitization is typically conducted after ESS given evidence that antecedent ESS improves aspirin treatment response and safety,^{67,68} any future high-risk surgical interventions may necessitate interruptions in treatment. Upcoming surgical procedures are also a common reason for discontinuation of ATAD, with some patients choosing not to resume therapy afterward.^{2,59}

Leukotriene Inhibition

Dysregulation of the production and proinflammatory activity of leukotrienes is central to the pathology of AERD, and leukotriene inhibition is often used as a therapeutic strategy in AERD. Leukotriene-modifying drugs include leukotriene receptor antagonists (montelukast, pranlukast, and zafirlukast) and 5-lipoxygenase (5-LO)

inhibitors (zileuton). Leukotriene inhibition has been repeatedly found to mitigate the severity of respiratory reactions experienced during aspirin challenge and desensitization.^{69–72}

For the longitudinal care of AERD, the addition of the leukotriene receptor antagonist montelukast has been found to improve asthma control, asthma-specific quality of life, and FEV₁, independent of baseline urinary LTE₄ levels.⁷³ Montelukast was also found to improve nasal function and nasal symptom scores in AERD.⁷⁴

Similarly, the addition of the 5-LO inhibitor zileuton to existing therapy (either inhaled or oral glucocorticoids) in AERD produced greater control of asthma symptoms, diminished nasal dysfunction, and inhibited aspirin-induced bronchoconstriction.⁷⁵ Subgroup analysis of the phase 3 studies for zileuton in asthma revealed that patients with aspirin-sensitive asthma had significantly greater improvements in pulmonary function after zileuton treatment, compared with aspirin-tolerant subjects,⁷⁶ underscoring the unique role of leukotriene dysregulation in AERD pathogenesis. Smaller retrospective studies also suggest that zileuton use in AERD may reduce the number of sinus surgeries required for management.^{77,78}

Biologic Therapy (Specific for Aspirin-Exacerbated Respiratory Disease)

Omalizumab

Omalizumab is a humanized IgG1k monoclonal antibody targeting free IgE that is currently approved in the United States and Europe for the treatment of severe asthma, CRSwNP, and chronic spontaneous urticaria. IgE likely has an important role in both mast cell activation and cysteinyl leukotriene overproduction in AERD,^{79,80} and elevation

Table 1

Summary of Outcomes From AERD Subgroup Analyses From Phase III Studies of Dupilumab, Mepolizumab, and Omalizumab for Treatment of CRSwNP

Drug/target	US FDA–approved indications	AERD participants in phase 3 CRSwNP studies (AERD/total # participants, percentage)	Primary outcomes from phase 3 CRSwNP studies	AERD subgroup analyses of phase 3 CRSwNP data
Omalizumab/IgE	Asthma, CRSwNP, chronic spontaneous urticaria	72/265 (27.2%)	Treatment arm mean differences at week 24: NPS: - POLYP 1: -1.14 (95% CI: -1.59 to -0.69; $P < .0001$) - POLYP 2: -0.59 (95% CI: -1.05 to -0.12; $P = .0140$) NCS: - POLYP 1: -0.55 (95% CI: -0.84 to -0.25; $P = .0004$) - POLYP 2: -0.50 (95% CI: -0.80 to -0.19; $P = .0017$) ⁸⁶ Adjusted difference in median at week 52: NPS: -0.73 (95% CI -1.11 to -0.34) Nasal obstruction VAS: -3.14 (95% CI -4.09 to -2.18) ⁸⁸	Adjusted mean difference in NCS, NPS, SNOT-22, and UPSIT change from baseline at week 24 favored omalizumab vs placebo in both patients with AERD and aspirin-tolerant CRSwNP ⁸⁷
Mepolizumab/IL-5	Asthma, CRSwNP, EGPA, HES	108/407 (27%)	Least squares mean change vs placebo at week 40: NPS: -0.57 (95% CI, -0.852 to -0.289; $P < .001$) NBS: -0.270 (95% CI, -0.458 to -0.083; $P < .005$) ⁹⁰ Least squares mean difference vs placebo at week 24: NPS: Sinus 24: -1.80 (95% CI: -2.43 to -1.69; $P < .0001$) Sinus 52: -2.06 (95% CI: -2.10 to -1.51; $P < .0001$) NCS: - Sinus 24: -0.87 (95% CI: -1.03 to -0.71; $P < .0001$) - Sinus 52: -0.89 (95% CI: -1.07 to -0.71; $P < .0001$) ⁹¹	Mepolizumab led to reduction in NPS, nasal obstruction VAS, need for surgery, and use of systemic corticosteroids in both patients with AERD and aspirin-tolerant CRSwNP ⁸⁹
Benralizumab/IL-5Rα	Asthma	121/413 (29.2%)		
Dupilumab/IL-4Rα	Asthma, CRSwNP, eosinophilic esophagitis, atopic dermatitis, prurigo nodularis	204/724 (28.2%)		Patients with AERD had significantly greater improvements with dupilumab than did aspirin-tolerant patients with CRSwNP for: nasal congestion, SNOT-22 scores, TSS, and PNIF. ⁹²

Abbreviations: AERD, aspirin-exacerbated respiratory disease; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyp; EGPA, eosinophilic granulomatosis with polyangiitis; FDA, Food and Drug Administration; HES, hypereosinophilic syndrome; IgE, immunoglobulin E; IL-5, interleukin-5; IL-4Rα, interleukin-4 receptor alpha; IL-5Rα, interleukin-5 receptor alpha; NCS, nasal congestion score, scale of 0 (no congestion) to 3 (severe congestion); nasal obstruction VAS, nasal obstruction visual analog scale, scale of 0 (no obstruction) to 10 (severe obstruction); NPS, endoscopic nasal polyp score measurement, scale of 0 (no polyps) to 8 (complete obstruction of nasal cavity bilaterally); PNIF, peak nasal inspiratory flow; SNOT, sinonasal outcome test; TSS, total symptom score; UPSIT, University of Pennsylvania Smell Identification Test; US, United States; VAS, visual analog scale.

in IgE levels is found in both patients with atopy and those without atopy but with AERD.⁸¹ Omalizumab treatment in AERD significantly reduces urinary LTE₄ and the stable urinary PGD₂ metabolite (PGD-M) concentrations.⁸² Omalizumab therapy has also been found to blunt aspirin-induced respiratory reactions during aspirin desensitization,⁸³ in addition to inhibiting urinary LTE₄ production during aspirin challenge. However, not all patients on omalizumab have blunted respiratory reactions to aspirin; therefore, patients on omalizumab should still undergo aspirin desensitization or challenge procedures in settings equipped to treat severe respiratory reactions.⁸⁴ Longitudinally, omalizumab treatment in AERD has been found to reduce the number of asthma exacerbations and hospitalizations, reduce daily inhaled and systemic corticosteroid doses, and improve patient-reported asthma symptom scores.^{82,85}

The efficacy and safety of omalizumab in nasal polyposis were evaluated in the POLYP1 and POLYP2 studies, replicate phase 3, randomized, double-blind placebo-controlled studies. Patients with AERD represented 27.2% of study participants. In these studies, omalizumab therapy significantly improved mean daily nasal congestion score (NCS) and nasal polyp score (NPS) in 24 weeks, in addition to improvements in the SNOT-22 score, University of Pennsylvania Smell Identification Test (UPSIT) score, and total nasal symptom score (TNSS)⁸⁶ (Table 1).

Mepolizumab and Benralizumab

Mepolizumab and benralizumab are humanized monoclonal antibodies targeting the IL-5 pathway, a key cytokine promoting respiratory tract eosinophilia in AERD.²⁸ Mepolizumab targets IL-5 directly, whereas benralizumab is an IL-5Rα antagonist. Mepolizumab is approved in the United States and Europe for the treatment of both severe asthma and nasal polyps. A higher dose of mepolizumab is approved for treatment of hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis.⁹³ Benralizumab is currently

approved for the treatment of severe eosinophilic asthma, and phase 3 studies of benralizumab for treatment of CRSwNP are ongoing (NCT04157335).

Mechanistically, mepolizumab treatment in AERD has been found to mitigate IL-5–mediated signaling on multiple immune cells (including mast cells, eosinophils, and epithelial cells), leading to significant decreases in peripheral blood eosinophilia, urinary tetranor PGD₂, and urinary LTE₄ concentrations.⁹⁴ Furthermore, the study investigators observed up-regulation in tight junction pathways and cilium organization in the nasal mucosa of patients with AERD treated with mepolizumab compared with patients not on a biologic (Fig 1).⁹⁴

From a clinical perspective, patients with AERD treated with mepolizumab have a significant improvement in nasal congestion, anosmia, and asthma control.⁹⁵ Subgroup analysis of the SYNPASE trial, the phase 3 study assessing safety efficacy of mepolizumab, included the 27% of patients in the original study who had AERD. Subgroup analysis revealed that compared with placebo, mepolizumab significantly reduced polyp size and nasal obstruction in patients with AERD.⁸⁹ Notably, however, mepolizumab treatment was not found to improve sense of smell as assessed by UPSIT.⁸⁹

The efficacy and safety of benralizumab for the treatment of CRSwNP were evaluated in the OSTRO study, a phase 3, randomized controlled trial in which 30% of patients in the intervention arm and 29.1% of patients in the placebo arm had AERD. Benralizumab was found to reduce NPS and nasal blockage score among patients with severe CRSwNP; subgroup analysis revealed similar improvements in NPS and nasal blockage score among those patients with AERD⁹⁰ (Table 1). In another randomized, double-blind, placebo-controlled trial of benralizumab for the treatment of CRSwNP (which included 46% participants self-reporting a history of aspirin sensitivity), benralizumab treatment improved SNOT-22 and UPSIT scores compared with placebo.⁹⁶ Benralizumab was similarly found to significantly reduce SNOT-22 scores among patients in a substudy of the ANDHI trial evaluating patients with severe asthma and nasal polyposis, in which 21.5% of the participants had a history of AERD.⁹⁷

The ANDHI substudy analysis also revealed that benralizumab significantly reduced annualized asthma exacerbation rate, in addition to improving ACQ-6 scores. However, in a real-life retrospective study of benralizumab for the treatment of severe eosinophilic asthma, the proportion of responders according to the Global Evaluation of Treatment score was lower among patients with AERD than those in the study without AERD.⁹⁸

Dupilumab

Dupilumab is a fully human monoclonal antibody targeting the alpha subunit of the IL-4 receptor. Dupilumab is currently approved by the Food and Drug Administration for the treatment of severe asthma and CRSwNP, including eosinophilic esophagitis, atopic dermatitis, and prurigo nodularis. Dupilumab treatment in AERD decreases levels of urinary LTE₄ and serum IgE and increases nasal levels of the anti-inflammatory prostaglandin PGE₂, in addition to down-regulating transcripts related to epithelial dysfunction and leukocyte dysfunction in nasal inferior turbinate tissue.⁹⁹ Furthermore, IL-4 and IL-13 are known to drive mucus overproduction (Fig 1).^{100,101}

A subgroup analysis of patients with AERD from 2 phase 3, randomized, controlled trials of dupilumab treatment for CRSwNP revealed broad clinical benefit of dupilumab, leading to significant improvements in NPS, SNOT-22 scores, total symptom scores, Lund-McKay CT scores, and ACQ scores (Table 1). Notably, the magnitude of this benefit of improvement for these parameters was greater in patients with AERD as compared with similar patients with CRSwNP without AERD.⁹² A reanalysis of patients with AERD in the phase 2 study assessing dupilumab for CRSwNP also revealed that compared with placebo, dupilumab significantly reduced NPS, improved SNOT-22 score, and increased FEV₁. In an open-label study of 22 patients with AERD treated with dupilumab, patients experienced rapid improvements in sinonasal symptoms and lung function within 1 month of starting dupilumab.⁹⁹ In a trial of 10 patients with AERD who had inadequately controlled sinus symptoms despite standard medical therapy, dupilumab as add-on treatment increased asthma control test and UPSIT scores.¹⁰² Taken together, these studies suggest that dupilumab is particularly effective in AERD, inducing rapid and broad improvements when used for patients with AERD.

Moreover, dupilumab seems to be also efficacious in patients who previously trialed other biologics. A retrospective analysis of patients with AERD who had inadequate response to IL-5 or IL-5R α targeting therapy revealed that dupilumab was effective for treatment of both upper and lower respiratory tract symptoms in this group.¹⁰³ A small retrospective study of 8 patients with AERD who previously had rapid recurrence of nasal polyps after ESS despite post-ESS treatment with ATAD revealed that perioperative treatment with dupilumab was effective in preventing nasal polyp recurrence and sinonasal symptoms.¹⁰⁴ Dupilumab also helps to improve alcohol-induced respiratory symptoms in AERD.¹⁰⁵

Although there are no completed head-to-head studies comparing respiratory biologic agents for patients with AERD or CRSwNP, retrospective analyses and meta-analyses suggest that dupilumab is particularly effective for patients with AERD. Analysis of patient-reported efficacy of biologics in AERD indicated that dupilumab had the highest odds patients reporting it worked “very well,” compared with others.² In a retrospective study of 74 patients with AERD who used at least 1 biologic, dupilumab treatment led to higher rates of clinical improvement in AERD compared with IL-5/IL-5R α and IgE targeting biologics.¹⁰⁶ In an indirect treatment comparison of the phase 3 studies of both omalizumab and dupilumab for treatment of CRSwNP, investigators found that dupilumab treatment led to significantly greater improvements in NPS, NCS, UPSIT, smell score, and total symptom score compared with omalizumab.¹⁰⁷ Finally, in a

large-network meta-analysis evaluating ATAD and biologics in CRSwNP, dupilumab was noted to be the most beneficial treatment for a wide spectrum of clinical outcomes.¹⁰⁸

Aspirin vs Biologic Therapy

With multiple highly efficacious biologic agents currently available for the treatment of severe asthma and CRSwNP in AERD, the optimal coordination of biologic therapy and ATAD is not yet defined. Both therapies were found to have benefit for the treatment of CRSwNP and asthma in patients with AERD.

ATAD is highly cost-effective and generally accessible to patients.¹⁰⁹ However, initiation of ATAD can be limited by the clinical availability and time required to facilitate desensitization. ATAD is preferentially started after ESS for safety and maximal benefit,^{17,18} which introduces additional challenges in coordinating timely care. Furthermore, ESS is resource intensive from the standpoint of health care utilization and lost productivity for the patient. In contrast, biologics can be started independent of surgical status and do not require periprocedural interruptions in care, as ATAD typically does.

Biologic therapies have a favorable safety profile in the short term,¹¹⁰ but limited longer-term safety data exist, with the exception of omalizumab. ATAD has multiple known adverse effects related to high-dose aspirin,^{54,64} and trials for efficacy and safety of ATAD are smaller and more limited in scope. Yet, the annual whole sale cost of biologics is substantial, typically in the range of approximately \$40,000 per year.¹¹¹ Although insurance coverage is able to substantially lower out-of-pocket costs for most patients, there remain notable disparities and inequities in access to biologic therapy among vulnerable and historically marginalized populations.⁵⁶ However, Sehanobish et al¹¹² observed a faster time to biologic approval for patients in the United States with public insurance compared with commercially insured patients, though time between prescription and first administration was similar. Many of the respiratory biologic agents are also approved for the treatment of other allergic/immunologic conditions (Table 1), which can coexist with AERD and provide some patients multiple benefits from respiratory biologic therapy.

There are currently no head-to-head studies comparing ATAD with biologic therapy in AERD. A recent network meta-analysis evaluated the comparative efficacy and safety of these treatments using data from 29 RCTs. Both biologics and ATAD were found to improve health-related quality of life, sinusitis symptoms, oral corticosteroid use, and nasal polyp size, with dupilumab and omalizumab resulting in improvement in the most categories assessed. However, biologics were noted to have an improved safety profile compared with aspirin desensitization and ATAD.¹⁰⁸

The recent Joint Task Force on Practice Parameters GRADE guidelines gave conditional recommendations for both the use of biologics for CRSwNP (moderate certainty of evidence) and ATAD for patients with AERD (moderate certainty of evidence).¹¹³ Recent expert opinion on the approach to the management of AERD proposes an initial trial of surgery and ATAD, with biologic initiation only after failure of these interventions.^{110,114} However, there is limited evidence to support this approach. One retrospective review of 103 patients with AERD revealed that ESS followed by ATAD was successful in the vast majority of cases,¹¹⁵ but in other studies, the efficacy of ATAD is less robust as discussed in the section Aspirin Desensitization.^{2,50} In a survey-based study, patients who ultimately started a biologic were less likely to have found ATAD effective for their AERD symptoms, suggesting that biologic therapy may occupy a role as a step-up from ATAD in the treatment of AERD.² However, despite these data, rates of aspirin desensitization among eligible patients are waning, in part because of the adoption of biologics.⁶²

The optimal coordination of ATAD, biologics, and surgery with consideration of cost, tolerability, and efficacy remains an important

clinical question. There is a pressing need for characterization of clinical phenotypes and biomarkers to better predict and understand likelihood of response to these therapies, and ultimately, inform best practices for care and shared decision making. At this time, physicians must use shared decision making, taking into account patient preference, comorbidities, individual clinical characteristics, and past treatment response to curate a personalized treatment plan for each individual with AERD.

Conclusion

The care of patients with AERD has evolved as our understanding of mechanisms underlying chronic respiratory tract inflammation has improved. The medical management of AERD is multifaceted and can require use of multiple therapeutic agents to achieve adequate control of both asthma and CRSwNP. For patients failing first-line, guideline-based treatment of asthma and CRSwNP, there are now multiple additional treatment options, including ATAD and respiratory biologic therapy. Future clinical and translational studies aimed to improve our understanding of mechanisms of these therapies, long-term safety, and individualized patient response will facilitate ongoing improvements in the care of patients with AERD.

Disclosures

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References

- White AA, Stevenson DD. Aspirin-exacerbated respiratory disease. *N Engl J Med*. 2018;379(11):1060–1070.
- Mullur J, Steger CM, Gakpo D, Bensko JC, Maurer R, Laidlaw TM, et al. Aspirin desensitization and biologics in aspirin-exacerbated respiratory disease: efficacy, tolerability, and patient experience. *Ann Allergy Asthma Immunol*. 2022;128(5):575–582.
- Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: a meta-analysis of the literature. *J Allergy Clin Immunol*. 2015;135(3):676–681.e1.
- Buchheit K, Bensko JC, Lewis E, Gakpo D, Laidlaw TM. The importance of timely diagnosis of aspirin-exacerbated respiratory disease for patient health and safety. *World J Otorhinolaryngol Head Neck Surg*. 2020;6(4):203–206.
- Stevens WW, Peters AT, Hirsch AG, Nordberg CM, Schwartz BS, Mercer DG, et al. Clinical characteristics of patients with chronic rhinosinusitis with nasal polyps, asthma, and aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2017;5(4):1061–1070.e3.
- Tuttle KL, Schneider TR, Henrickson SE, Morris D, Abonia JP, Spergel JM, et al. Aspirin-exacerbated respiratory disease: not always “adult-onset”. *J Allergy Clin Immunol Pract*. 2016;4(4):756–758.
- Bensko JC, McGill A, Palumbo M, Cahill KN, Laidlaw TM. Pediatric-onset aspirin-exacerbated respiratory disease: clinical characteristics, prevalence, and response to dupilumab. *J Allergy Clin Immunol Pract*. 2022;10(9):2466–2468.
- Bassiouni A, Wormald PJ. Role of frontal sinus surgery in nasal polyp recurrence. *Laryngoscope*. 2013;123(1):36–41.
- McMains KC, Kountakis SE. Medical and surgical considerations in patients with Samter’s triad. *Am J Rhinol*. 2006;20(6):573–576.
- DeGregorio GA, Singer J, Cahill KN, Laidlaw T. A 1-day, 90-minute Aspirin challenge and desensitization protocol in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2019;7(4):1174–1180.
- Pelletier T, Roizen G, Ren Z, Hudes G, Rosenstreich D, Jerschow E. Comparable safety of 2 aspirin desensitization protocols for aspirin exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2019;7(4):1319–1321.
- Cahill KN, Bensko JC, Boyce JA, Laidlaw TM. Prostaglandin D₂: a dominant mediator of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2015;135(1):245–252.
- Stevenson DD, White AA, Simon RA. Aspirin as a cause of pancreatitis in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2012;129(6):1687–1688.
- De Schryver E, Derycke L, Campo P, Gabriels E, Joos GF, Van Zele T, et al. Alcohol hyper-responsiveness in chronic rhinosinusitis with nasal polyps. *Clin Exp Allergy*. 2017;47(2):245–253.
- Cardet JC, White AA, Barrett NA, Feldweg AM, Wickner PG, Savage J, et al. Alcohol-induced respiratory symptoms are common in patients with aspirin exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2014;2(2):208–213.
- Kowalski ML, Makowska JS. Seven steps to the diagnosis of NSAIDs hypersensitivity: how to apply a new classification in real practice? *Allergy Asthma Immunol Res*. 2015;7(4):312–320.
- Jerschow E, Edin ML, Chi Y, Hurst B, Abuzeid WM, Akbar NA, et al. Sinus surgery is associated with a decrease in aspirin-induced reaction severity in patients with aspirin exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2019;7(5):1580–1588.
- Huang GX, Palumbo ML, Singer JI, Cahill KN, Laidlaw TM. Sinus surgery improves lower respiratory tract reactivity during aspirin desensitization for AERD. *J Allergy Clin Immunol Pract*. 2019;7(5):1647–1649.
- Comhair SAA, Bochenek G, Baicker-McKee S, Wang Z, Stachura T, Sanak M, et al. The utility of biomarkers in diagnosis of aspirin exacerbated respiratory disease. *Respir Res*. 2018;19(1):210.
- Laidlaw TM, Boyce JA. Updates on immune mechanisms in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2023;151(2):301–309.
- Lyly A, Laidlaw TM, Lundberg M. Pathomechanisms of AERD—recent advances. *Front Allergy*. 2021;2:734733.
- Eid R, Yan CH, Stevens W, Doherty TA, Borish L. Innate immune cell dysregulation drives inflammation and disease in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2021;148(2):309–318.
- Stevens WW, Staudacher AG, Hulse KE, Poposki JA, Kato A, Carter RG, et al. Studies of the role of basophils in aspirin-exacerbated respiratory disease pathogenesis. *J Allergy Clin Immunol*. 2021;148(2):439–449.e5.
- Dwyer DF, Ordovas-Montanes J, Allon SJ, Buchheit KM, Vukovic M, Derakhshan T, et al. Human airway mast cells proliferate and acquire distinct inflammation-driven phenotypes during type 2 inflammation. *Sci Immunol*. 2021;6(56):eabb7221.
- Mahdavinia M, Carter RG, Ocampo CJ, Stevens W, Kato A, Tan BK, et al. Basophils are elevated in nasal polyps of patients with chronic rhinosinusitis without aspirin sensitivity. *J Allergy Clin Immunol*. 2014;133(6):1759–1763.
- Nasser SM, Pfister R, Christie PE, Sousa AR, Barker J, Schmitz-Schumann M, et al. Inflammatory cell populations in bronchial biopsies from aspirin-sensitive asthmatic subjects. *Am J Respir Crit Care Med*. 1996;153(1):90–96.
- Buchheit KM, Hulse KE. Local immunoglobulin production in nasal tissues: A key to pathogenesis in chronic rhinosinusitis with nasal polyps and aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2021;126(2):127–134.
- Buchheit KM, Dwyer DF, Ordovas-Montanes J, Katz HR, Lewis E, Vukovic M, et al. IL-5Rα marks nasal polyp IgG4- and IgE-expressing cells in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2020;145(6):1574–1584.
- Laidlaw TM, Kidder MS, Bhattacharyya N, Xing W, Shen S, Milne GL, et al. Cysteinyl leukotriene overproduction in aspirin-exacerbated respiratory disease is driven by platelet-adherent leukocytes. *Blood*. 2012;119(16):3790–3798.
- Balzar S, Fajt ML, Comhair SA, Erzurum SC, Bleecker E, Busse WW, et al. Mast cell phenotype, location, and activation in severe asthma. Data from the Severe Asthma Research Program. *Am J Respir Crit Care Med*. 2011;183(3):299–309.
- Oskeritzian CA, Zhao W, Min HK, Xia HZ, Pozze A, Kiev J, et al. Surface CD88 functionally distinguishes the MCTC from the MCT type of human lung mast cell. *J Allergy Clin Immunol*. 2005;115(6):1162–1168.
- Cavagnero KJ, Doherty TA. Lipid-mediated innate lymphoid cell recruitment and activation in aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2021;126(2):135–142.
- Buchheit KM, Cahill KN, Katz HR, Murphy KC, Feng C, Lee-Sarwar K, et al. Thymic stromal lymphopoietin controls prostaglandin D₂ generation in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2016;137(5):1566–1576.e5.
- Pan D, Buchheit KM, Samuchiwal SK, Liu T, Cirka H, Raff H, et al. COX-1 mediates IL-33-induced extracellular signal-regulated kinase activation in mast cells: implications for aspirin sensitivity. *J Allergy Clin Immunol*. 2019;143(3):1047–1057.e8.
- Liu T, Kanaoka Y, Barrett NA, Feng C, Garofalo D, Lai J, et al. Aspirin-exacerbated respiratory disease involves a cysteinyl leukotriene-driven IL-33-mediated mast cell activation pathway. *J Immunol*. 2015;195(8):3537–3545.
- Van Zele T, Gevaert P, Watelet JB, Claeys G, Holtappels G, Claeys C, et al. Staphylococcus aureus colonization and IgE antibody formation to enterotoxins is increased in nasal polyposis. *J Allergy Clin Immunol*. 2004;114(4):981–983.
- Scott WC, Cahill KN, Milne GL, Li P, Sheng Q, Huang LC, et al. Inflammatory heterogeneity in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2021;147(4):1318–1328.e5.
- Corey KB, Turner JH, Chowdhury NI, Chandra RK, Li P, Wu P, et al. Utility of nasal mucus inflammatory profile as a biomarker of nasal polyp regrowth in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2022;10(6):1644–1645.e1.
- Sladek K, Dworski R, Soja J, Sheller JR, Nizankowska E, Oates JA, et al. Eicosanoids in bronchoalveolar lavage fluid of aspirin-intolerant patients with asthma after aspirin challenge. *Am J Respir Crit Care Med*. 1994;149(4, pt 1):940–946.
- Bochenek G, Nagraba K, Nizankowska E, Szczeklik A. A controlled study of 9α,11β-PGF₂ (a prostaglandin D₂ metabolite) in plasma and urine of patients with bronchial asthma and healthy controls after aspirin challenge. *J Allergy Clin Immunol*. 2003;111(4):743–749.

41. Yoshimura T, Yoshikawa M, Otori N, Haruna S, Moriyama H. Correlation between the prostaglandin D(2)/E(2) ratio in nasal polyps and the recalcitrant pathophysiology of chronic rhinosinusitis associated with bronchial asthma. *Allergol Int*. 2008;57(4):429–436.
42. Laidlaw TM, Boyce JA. Aspirin-exacerbated respiratory disease—new prime suspects. *N Engl J Med*. 2016;374(5):484–488.
43. Christie PE, Tagari P, Ford-Hutchinson AW, Charlesson S, Chee P, Arm JP, et al. Urinary leukotriene E4 concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. *Am Rev Respir Dis*. 1991;143(5, pt 1):1025–1029.
44. Mastalerz L, Sanak M, Gawlewicz-Mroccka A, Gielicz A, Cmiel A, Szczeklik A. Prostaglandin E2 systemic production in patients with asthma with and without aspirin hypersensitivity. *Thorax*. 2008;63(1):27–34.
45. Sestini P, Armetti L, Gambaro G, Pieroni MG, Refini RM, Sala A, et al. Inhaled PGE2 prevents aspirin-induced bronchoconstriction and urinary LTE4 excretion in aspirin-sensitive asthma. *Am J Respir Crit Care Med*. 1996;153(2):572–575.
46. Stevenson DD, Pleskow WW, Simon RA, Mathison DA, Lumry WR, Schatz M, et al. Aspirin-sensitive rhinosinusitis asthma: a double-blind crossover study of treatment with aspirin. *J Allergy Clin Immunol*. 1984;73(4):500–507.
47. Stevenson DD, Simon RA, Mathison DA. Aspirin-sensitive asthma: tolerance to aspirin after positive oral aspirin challenges. *J Allergy Clin Immunol*. 1980;66(1):82–88.
48. Lee JY, Simon RA, Stevenson DD. Selection of aspirin dosages for aspirin desensitization treatment in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2007;119(1):157–164.
49. Stevens WW, Jerschow E, Baptist AP, Borish L, Bosso JV, Buchheit KM, et al. The role of aspirin desensitization followed by oral aspirin therapy in managing patients with aspirin-exacerbated respiratory disease: A Work Group Report from the Rhinitis, Rhinosinusitis and Ocular Allergy Committee of the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2021;147(3):827–844.
50. Cahill KN, Cui J, Kothari P, Murphy K, Raby BA, Singer J, et al. Unique effect of aspirin therapy on biomarkers in aspirin-exacerbated respiratory disease. A prospective trial. *Am J Respir Crit Care Med*. 2019;200(6):704–711.
51. Borish L. Aspirin-exacerbated respiratory disease: A syndrome of mast cell-mediated PgD2 overproduction. *Am J Respir Crit Care Med*. 2019;200(6):651–652.
52. Świerczyńska-Krepa M, Sanak M, Bochenek G, Stręk P, Cmiel A, Gielicz A, et al. Aspirin desensitization in patients with aspirin-induced and aspirin-tolerant asthma: a double-blind study. *J Allergy Clin Immunol*. 2014;134(4):883–890.
53. Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. *J Allergy Clin Immunol*. 1996;98(4):751–758.
54. Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2003;111(1):180–186.
55. Fruth K, Pogorzelski B, Schmidtmann I, Springer J, Fennan N, Fraessdorf N. Low-dose aspirin desensitization in individuals with aspirin-exacerbated respiratory disease. *Allergy*. 2013;68(5):659–665.
56. Akenroye AT, Heyward J, Keet C, Alexander GC. Lower use of biologics for the treatment of asthma in publicly insured individuals. *J Allergy Clin Immunol Pract*. 2021;9(11):3969–3976.
57. Mortazavi N, Esmailzadeh H, Abbasiazari M, Babaie D, Alyasin S, Nabavizadeh H, et al. Clinical and immunological efficacy of aspirin desensitization in nasal polyp patients with aspirin-exacerbated respiratory disease. *Iran J Pharm Res*. 2017;16(4):1639–1647.
58. Esmailzadeh H, Nabavi M, Aryan Z, Arshi S, Bemanian MH, Fallahpour M, et al. Aspirin desensitization for patients with aspirin-exacerbated respiratory disease: a randomized double-blind placebo-controlled trial. *Clin Immunol*. 2015;160(2):349–357.
59. Walters KM, Waldram JD, Woessner KM, White AA. Long-term clinical outcomes of aspirin desensitization with continuous daily aspirin therapy in aspirin-exacerbated respiratory disease. *Am J Rhinol Allergy*. 2018;32(4):280–286.
60. Mathison DA, Lumry W, Stevenson D, Curd J. Aspirin in chronic urticaria and/or angioedema: studies of sensitivity and desensitization. *J Allergy Clin Immunol*. 1982;69(1):135.
61. Waldram JD, White AA. A survey of aspirin desensitization practices among allergists and fellows in training in the United States. *J Allergy Clin Immunol Pract*. 2016;4(6):1253–1255.
62. White AA. If aspirin-exacerbated respiratory disease treatment is a jigsaw puzzle, where do the aspirin and biologic pieces go? *Ann Allergy Asthma Immunol*. 2022;128(5):484–485.
63. White AA, Woessner K, Simon R. Aspirin-exacerbated respiratory disease: update on medical management. *World J Otorhinolaryngol Head Neck Surg*. 2020;6(4):241–247.
64. Chu DK, Lee DJ, Lee KM, Schünemann HJ, Szczeklik W, Lee JM. Benefits and harms of aspirin desensitization for aspirin-exacerbated respiratory disease: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. 2019;9(12):1409–1419.
65. Jerschow E, Edin ML, Pelletier T, Abuzeid WM, Akbar NA, Gibber M, et al. Plasma 15-hydroxyeicosatetraenoic acid predicts treatment outcomes in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2017;5(4):998–1007.e2.
66. Guirguis-Blake JM, Evans CV, Perdue LA, Bean SI, Senger CA. Aspirin use to prevent cardiovascular disease and colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. [published correction appears in *JAMA*. 2022;327(22):2249] *JAMA*. 2022;327(16):1585–1597.
67. Levy JM, Rudmik L, Peters AT, Wise SK, Rotenberg BW, Smith TL. Contemporary management of chronic rhinosinusitis with nasal polyposis in aspirin-exacerbated respiratory disease: an evidence-based review with recommendations. *Int Forum Allergy Rhinol*. 2016;6(12):1273–1283.
68. Shah SJ, Abuzeid WM, Ponduri A, Pelletier T, Ren Z, Keskin T, et al. Endoscopic sinus surgery improves aspirin treatment response in aspirin-exacerbated respiratory disease patients. *Int Forum Allergy Rhinol*. 2019;9(12):1401–1408.
69. White AA, Stevenson DD, Simon RA. The blocking effect of essential controller medications during aspirin challenges in patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2005;95(4):330–335.
70. Berges-Gimeno MP, Simon RA, Stevenson DD. The effect of leukotriene-modifier drugs on aspirin-induced asthma and rhinitis reactions. *Clin Exp Allergy*. 2002;32(10):1491–1496.
71. Park JS, Jang AS, Park SW, Lee YM, Uh ST, Kim YH, et al. Protection of leukotriene receptor antagonist against aspirin-induced bronchospasm in asthmatics. *Allergy Asthma Immunol Res*. 2010;2(1):48–54.
72. Ramírez-Jiménez F, Vázquez-Corona A, Sánchez-de la Vega Reynoso P, Pavón-Romero GF, Jiménez-Chobillon MA, Castorena-Maldonado AR, et al. Effect of LTRA in L-ASA Challenge for aspirin-exacerbated respiratory disease diagnosis. *J Allergy Clin Immunol Pract*. 2021;9(4):1554–1561.
73. Dahlén SE, Malmström K, Nizankowska E, Dahlén B, Kuna P, Kowalski M, et al. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med*. 2002;165(1):9–14.
74. Micheletto C, Tognella S, Visconti M, Pomari C, Trevisan F, Dal Negro RW. Montelukast 10 mg improves nasal function and nasal response to aspirin in ASA-sensitive asthmatics: a controlled study vs placebo. *Allergy*. 2004;59(3):289–294.
75. Dahlén B, Nizankowska E, Szczeklik A, Zetterström O, Bochenek G, Kumlin M, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med*. 1998;157(4, pt 1):1187–1194.
76. Laidlaw TM, Fuentes DJ, Wang Y. Efficacy of zileuton in patients with asthma and history of aspirin sensitivity: a retrospective analysis of data from two Phase 3 studies. *J Allergy Clin Immunol*. 2017;139(2):AB384.
77. Lee SE, Farquhar DR, Adams KN, Masood MM, Senior BA, Thorp BD, et al. Effect of zileuton treatment on sinonasal quality of life in patients with aspirin-exacerbated respiratory disease. *Am J Rhinol Allergy*. 2019;33(6):791–795.
78. Makary CA, Holmes T, Unsal A, Munjal A, Ryan L, Reyes C, et al. Long-term role of zileuton in the treatment of chronic rhinosinusitis in aspirin exacerbated respiratory disease. *Am J Otolaryngol*. 2022;43(1): 103227.
79. Busse WW. Does IgE have a role in aspirin-exacerbated respiratory disease? *Am J Respir Crit Care Med*. 2020;201(12):1459–1460.
80. Taniguchi M, Heffler E, Olze H, White A, Corte-Real J, Olsson P, et al. The role of omalizumab in NSAID-exacerbated respiratory disease: A narrative review. *J Allergy Clin Immunol Pract*. 2022;10(10):2570–2578.
81. Johns CB, Laidlaw TM. Elevated total serum IgE in nonatopic patients with aspirin-exacerbated respiratory disease. *Am J Rhinol Allergy*. 2014;28(4):287–289.
82. Hayashi H, Mitsui C, Nakatani E, Fukutomi Y, Kajiwaru K, Watai K, et al. Omalizumab reduces cysteinyl leukotriene and 9α,11β-prostaglandin F2 overproduction in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2016;137(5):1585.e4.
83. Lang DM, Aronica MA, Maierson ES, Wang XF, Vasas DC, Hazen SL. Omalizumab can inhibit respiratory reaction during aspirin desensitization. *Ann Allergy Asthma Immunol*. 2018;121(1):98–104.
84. Waldram J, Walters K, Simon R, Woessner K, Waalen J, White A. Safety and outcomes of aspirin desensitization for aspirin-exacerbated respiratory disease: A single-center study. *J Allergy Clin Immunol*. 2018;141(1):250–256.
85. Jean T, Eng V, Sheikh J, Kaplan MS, Goldberg B, Jau Yang S, et al. Effect of omalizumab on outcomes in patients with aspirin-exacerbated respiratory disease. *Allergy Asthma Proc*. 2019;40(5):316–320.
86. Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. [published correction appears in *J Allergy Clin Immunol*. 2021;147(1):416] *J Allergy Clin Immunol*. 2020;146(3):595–605.
87. Damask C, Chen M, Holweg CTJ, Yoo B, Millette LA, Franzese C. Defining the efficacy of omalizumab in nasal polyposis: a POLYP 1 and POLYP 2 subgroup analysis. *Am J Rhinol Allergy*. 2022;36(1):135–141.
88. Han JK, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2021;9(10):1141–1153.
89. Bachert C, Sousa AR, Han JK, Schlosser RJ, Sowerby LJ, Hopkins C, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps: treatment efficacy by comorbidity and blood eosinophil count. *J Allergy Clin Immunol*. 2022;149(5):1711–1721.e6.
90. Bachert C, Han JK, Desrosiers MY, Gevaert P, Heffler E, Hopkins C, et al. Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: A randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2022;149(4):1309–1317.e12.
91. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. 2019;394(10209):1638–1650.
92. Mullol J, Laidlaw TM, Bachert C, Mannent LP, Canonica GW, Han JK, et al. Efficacy and safety of dupilumab in patients with uncontrolled severe chronic rhinosinusitis with nasal polyps and a clinical diagnosis of NSAID-ERD: results from two randomized placebo-controlled phase 3 trials. *Allergy*. 2022;77(4):1231–1244.

93. Food and Drug Administration. Highlights of prescribing information: NUCALA (mepolizumab). https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF. Accessed March 3, 2023.
94. Buchheit KM, Lewis E, Gakpo D, Hacker J, Sohail A, Taliaferro F, et al. Mepolizumab targets multiple immune cells in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2021;148(2):574–584.
95. Tuttle KL, Buchheit KM, Laidlaw TM, Cahill KN. A retrospective analysis of mepolizumab in subjects with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2018;6(3):1045–1047.
96. Tversky J, Lane AP, Azar A. Benralizumab effect on severe chronic rhinosinusitis with nasal polyps (CRSwNP): A randomized double-blind placebo-controlled trial. *Clin Exp Allergy*. 2021;51(6):836–844.
97. Canonica GW, Harrison TW, Chanez P, Menzella F, Louis R, Cosio BG, et al. Benralizumab improves symptoms of patients with severe, eosinophilic asthma with a diagnosis of nasal polyposis. *Allergy*. 2022;77(1):150–161.
98. Numata T, Miyagawa H, Nishioka S, Okuda K, Utsumi H, Hashimoto M, et al. Efficacy of benralizumab for patients with severe eosinophilic asthma: a retrospective, real-life study. *BMC Pulm Med*. 2020;20(1):207.
99. Buchheit KM, Sohail A, Hacker J, Maurer R, Gakpo D, Bensko JC, et al. Rapid and sustained effect of dupilumab on clinical and mechanistic outcomes in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2022;150(2):415–424.
100. Zhu Z, Homer RJ, Wang Z, Chen Q, Geba GP, Wang J, et al. Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiologic abnormalities, and eotaxin production. *J Clin Invest*. 1999;103(6):779–788.
101. Temann UA, Prasad B, Gallup MW, Basbaum C, Ho SB, Flavell RA, et al. A novel role for murine IL-4 in vivo: induction of MUC5AC gene expression and mucin hypersecretion. *Am J Respir Cell Mol Biol*. 1997;16(4):471–478.
102. Mustafa SS, Vadimalai K, Scott B, Ramsey A. Dupilumab as add-on therapy for chronic rhinosinusitis with nasal polyposis in aspirin exacerbated respiratory disease. *Am J Rhinol Allergy*. 2021;35(3):399–407.
103. Bavaro N, Gakpo D, Mittal A, Bensko JC, Laidlaw TM, Buchheit KM. Efficacy of dupilumab in patients with aspirin-exacerbated respiratory disease and previous inadequate response to anti-IL-5 or anti-IL-5R α in a real-world setting. *J Allergy Clin Immunol Pract*. 2021;9(7):2910–2912.e1.
104. Patel P, Bensko JC, Bhattacharyya N, Laidlaw TM, Buchheit KM. Dupilumab as an adjunct to surgery in patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2022;128(3):326–328.
105. Arnold M, Kuruville M, Levy JM, Xu J. Dupilumab improves alcohol tolerance in aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2021;127(3):379–381.
106. Wangberg H, Spierling Bagsic SR, Osuna L, White AA. Appraisal of the real-world effectiveness of biologic therapies in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2022;10(2):478–484.e3.
107. Peters AT, Han JK, Hellings P, Heffler E, Gevaert P, Bachert C, et al. Indirect treatment comparison of biologics in chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol Pract*. 2021;9(6):2461–2471.e5.
108. Oykhman P, Paramo FA, Bousquet J, Kennedy DW, Brignardello-Petersen R, Chu DK. Comparative efficacy and safety of monoclonal antibodies and aspirin desensitization for chronic rhinosinusitis with nasal polyposis: A systematic review and network meta-analysis. *J Allergy Clin Immunol*. 2022;149(4):1286–1295.
109. Shaker M, Lobb A, Jenkins P, O'Rourke D, Takemoto SK, Sheth S, et al. An economic analysis of aspirin desensitization in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2008;121(1):81–87.
110. Laidlaw TM, Chu DK, Stevens WW, White AA. Controversies in allergy: aspirin desensitization or biologics for aspirin-exacerbated respiratory disease-how to choose. *J Allergy Clin Immunol Pract*. 2022;10(6):1462–1467.
111. Workman AD, Bleier BS. Biologic therapies versus surgical management for aspirin-exacerbated respiratory disease: a review of preliminary data, efficacy, and cost. *World J Otorhinolaryngol Head Neck Surg*. 2020;6(4):230–234.
112. Sehanobish E, Ye K, Imam K, et al. Elaborate biologic approval process delays care of patients with moderate-to-severe asthma. *J Allergy Clin Immunol Glob*. 2023;2(2): 100076.
113. Rank MA, Chu DK, Bognanni A, Oykhman P, Bernstein JA, Ellis AK, et al. The Joint Task Force on Practice Parameters GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis. *J Allergy Clin Immunol*. 2023;151(2):386–398.
114. Buchheit KM, Laidlaw TM, Levy JM. Immunology-based recommendations for available and upcoming biologics in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2021;148(2):348–350.
115. Sweis AM, Locke TB, Ig-Izevbekhai KI, Lin TC, Kumar A, Douglas JE, et al. Effectiveness of endoscopic sinus surgery and aspirin therapy in the management of aspirin-exacerbated respiratory disease. *Allergy Asthma Proc*. 2021;42(2):136–141.