

Nasal Polyposis and Aspirin-Exacerbated Respiratory Disease

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KEYWORDS

• Nasal • Polyp • AERD • Aspirin • Exacerbated • Respiratory • disease

KEY POINTS

- Aspirin-exacerbated respiratory disease (AERD) is characterized by persistent and difficult-to-treat nasal polyposis, eosinophilic chronic sinusitis, asthma, and nonsteroidal anti-inflammatory drug reactions and is often accompanied by alcohol sensitivity.
- The underlying pathophysiology of AERD seems to involve dysregulated arachidonic acid metabolism and receptor signaling, along with eosinophil and mast cell byproducts, including increased leukotriene E4 and prostaglandin D2 and decreased prostaglandin E2.
- There are a variety of therapies available for AERD, including those that interfere with leukotriene production or signaling, topical and systemic corticosteroids, biologics, dietary modification, and aspirin.
- Aspirin challenge is the gold standard for AERD diagnosis, and desensitization provides a unique and effective therapeutic alternative; the decision about procedure timing and location must be individualized based on patient factors.
- Aspirin therapy is generally well tolerated, although side effects and lack of response or maintenance of desensitization can occur in a minority of patients.

INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) is seen in a subset of patients with nasal polyposis who have comorbid asthma and acute upper and lower respiratory tract reactions with exposure to aspirin (acetylsalicylic acid) or other cyclooxygenase-1 (COX-1)-inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs).

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AERD is usually diagnosed in the third or fourth decades of life, with approximately 50% of patients reporting a viral syndrome at initiation. Reactions to aspirin/NSAIDs depend on inhibition of the COX-1 enzyme inhibition rather than being immunoglobulin E (IgE) mediated. NSAID tolerance before the development of NSAID reactions is typical. Although NSAID hypersensitivity can precede respiratory disease, most patients develop asthma and chronic rhinosinusitis with nasal polyposis (CRSwNP) first, with NSAID reactions occurring later in the disease. NSAID reactions occur typically between 30 minutes and 3 hours after ingestion, and severity may be dose-related.¹ Typical reactions include nasal congestion, rhinorrhea, ocular pruritis with erythema, and bronchospasm.² Less commonly, cutaneous (rash and flushing) or gastrointestinal symptoms (abdominal pain, diarrhea, vomiting) can be the predominant findings.³

ASPIRIN-EXACERBATED RESPIRATORY DISEASE BURDEN

Approximately 7.9% of the US population has asthma, and among adult asthmatic patients, about 7% have AERD, with the prevalence increasing to 30% in patients with asthma and nasal polyps.⁴⁻⁶ There are significant financial, physical, and emotional costs in AERD, in part due to the severity and persistence of their sinus and airway disease.⁷

In 2013, it was estimated reported that the total cost of asthma in the United States was \$81.9 billion.⁸ Poor asthma control was associated with a greater prevalence of sleep problems, depression, functional impairment, and negative impact on work and regular activities.⁹ Although patients with AERD comprise a small portion of all patients with asthma, they tend to have more severe and poorly-controlled disease requiring aggressive therapy. Compared with non-AERD asthmatics, patients with AERD had higher rates of intubation and high-dose inhaled corticosteroid use and lower mean post-bronchodilator forced expiratory volume at 1 second (FEV1).¹⁰ In addition to asthma, patients with AERD have severe sinus disease, with 10 times as many functional endoscopic sinus surgeries (FESS) and higher rates of polyp recurrence than non-AERD patients.¹¹ Patients with AERD likely comprise a significant portion of the \$3.4 to 5 billion annual cost of CRS.¹² Chronic nasal symptoms, anosmia, and inability to enjoy eating contribute to poor quality of life in AERD.¹³

Although CRSwNP and asthma have significant disease-associated financial costs and morbidity, the AERD subgroup bears a disproportionate burden of disease and medical utilization. Given the high burden of disease, it is imperative to identify impactful, cost-effective therapies.

Alcohol Reactivity in Aspirin-Exacerbated Respiratory Disease

Alcohol sensitivity was first described in 1986, when asthmatic patients developed alcohol-induced respiratory reactions after ingestion of red wine.^{14,15} NSAID intolerance was identified in 17% of patients with alcohol-induced nasal symptoms.¹⁶ One study demonstrated the prevalence of alcohol-induced reactions were significantly higher in patients with AERD (75%) compared with aspirin-tolerant asthmatics (33%), CRS (30%), and healthy controls (14%).¹⁷ Similar prevalence was reported in a survey, where 77% of the 190 AERD respondents reported alcohol reactivity.¹³

The mechanism for alcohol reactivity is unknown, although it is suspected that cysteinyl leukotrienes (CysLTs) or other mast cell mediators play a key role in these reactions.¹⁷ Alcohol sensitivity as a manifestation of the underlying inflammatory milieu of AERD is supported by the finding that the severity of aspirin-induced reactions positively correlated with the severity of alcohol-induced reactions.¹⁷ Moreover, aspirin desensitization has been shown to improve alcohol-induced respiratory reactions in AERD.¹⁸

Inflammatory Basis of Aspirin-Exacerbated Respiratory Disease

Since AERD was originally identified, there has been an increased understanding of disease pathophysiology. Mechanisms underlying AERD are thought to involve abnormal arachidonic acid metabolism, overproduction of CysLTs and pro-inflammatory prostaglandins, and underproduction of the anti-inflammatory prostaglandin PGE₂.³

The role of CysLTs is evidenced by studies that have demonstrated improvement in anosmia, polyp size, and FEV1 that corresponded to a decrease in urine LTE₄ (uLTE₄) seen with leukotriene modifier drugs.¹⁹ Patients with AERD have increased CysLT burden and responsiveness in AERD, with an increase in CysLT1 receptors and heightened airway sensitivity to LTE₄ compared with aspirin-tolerant patients.^{20,21} Aspirin reactions are characterized by increased uLTE₄, and those with more severe reactions have higher baseline and larger increase in uLTE₄.^{3,22,23}

It is not known whether LTE₄ causes bronchoconstriction directly or whether it acts through prostaglandin production, especially prostaglandin D₂ (PGD₂). PGD₂ is found in high levels in mast cells and promotes vasodilation, bronchoconstriction, and eosinophil and basophil chemotaxis. Mast cell functionality cells in AERD is supported by the increase in tryptase with aspirin reactions and the observation that cromolyn improves nasal symptoms and FEV1 at baseline and with aspirin challenge.^{24–26} Leukotrienes result in mast cell PGD₂ production, either directly through LTE₄ binding to CysLT1 receptor or indirectly via binding epithelial GPR99 receptors that subsequently cause mast cell activation.^{27–29} Although PGD₂ is a primary mast cell mediator, in AERD eosinophils have high hematopoietic prostaglandin D synthase expression and can be stimulated by aspirin to produce PGD₂.³⁰ In addition, eosinophils demonstrate production of and response to interferon gamma (IFN- γ), which may augment the pro-inflammatory state in AERD.³¹ The balance of pro- to anti-inflammatory molecules is important, and antiinflammatory PGE₂ seems to be protective. Lower PDG₂:PGE₂ ratio, less peripheral eosinophilia, and attenuated increase in uLTE₄ was found in post-polypectomy AERD patients who underwent re-challenge and did not react compared with those who reacted.³² Moreover, polyps seem to be physiologically active inflammatory tissue as evidenced by a decrease in aspirin challenge reaction rate and severity; increase in plasma lipoxin A; and decrease in baseline uLTE₄, PGD₂ metabolite, and FeNO in post- versus pre-surgery AERD subjects.³²

Several other discoveries shed light on unique inflammatory pathways involved in AERD. Adherent platelets on leukocytes can form a unit that augments the production of cysLTs in AERD.³³ Type 2 innate lymphocytes (ILC2) traffic to the sinuses during aspirin-induced reactions and may contribute to inflammation in AERD.³⁴ In addition to the different cell recruitment and function, signaling may be abnormal in AERD. Aberrant LTE₄ signaling through recently described receptors, GPR99 and P2Y₁₂, in addition to CysLT1/2 are avenues for further study.^{35–37} Although the underlying phenotype of nasal polyposis, eosinophilia, and asthma may be indistinguishable across the spectrum, the pathophysiology of AERD is distinct and has unique inflammatory characteristics.

MEDICAL MANAGEMENT OF ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Given the overproduction of the CysLTs in AERD, medications mitigating the effects of these molecules are cornerstones of the AERD therapeutic regimen and improve safety in aspirin desensitization.^{38,39} There are 2 identified leukotriene receptor antagonists (LTRA), montelukast and zafirlukast, which block the CysLT1 receptor

but have minimal effects on leukotriene B₄ (LTB₄) and LTE₄ signaling. Zileuton is a 5-lipoxygenase (5-LO) inhibitor that blocks the synthesis of both CysLTs and LTB₄. Montelukast improves lung function, reduces bronchodilator use and asthma exacerbations, improves quality of life, decreases nasal polyp eosinophilia, and improves nasal symptom scores.^{40,41} Zileuton improves pulmonary function and nasal inspiratory flow, increases sense of smell, and decreases rhinorrhea in patients with AERD.¹⁹ Zileuton, which may be more potent than LTRA, may be underused in AERD.^{13,42}

Corticosteroids are important components of AERD treatment. Intranasal glucocorticoids may be helpful in preventing polyp regrowth after sinus surgery in AERD, but not all studies demonstrate efficacy, and polyp recurrence continues to be problematic.^{43–45} Fluticasone propionate is available in a new Food and Drug Administration–approved delivery device (Xhance) and decreased nasal polyp size and improved quality-of-life and symptoms in CRSwNP but was not specifically studied in AERD.⁴⁶ Nasal rinses with budesonide respules are also used for the reduction of nasal polyps and are effective in reducing sinus computed tomographic scores, symptoms, and anosmia in those with chronic eosinophilic sinusitis.⁴⁷ Budesonide rinses have not been specifically studied in AERD.

Other therapies for patients with AERD are being studied. This includes platelet-targeted therapies, including a P2Y₁₂-receptor antagonist and a thromboxane receptor (TP) antagonist. Although a treatment effect was not seen in AERD overall, a P2Y₁₂ inhibitor was effective in inhibiting aspirin-induced symptoms in a subgroup of patients who had greater baseline platelet activation and milder upper respiratory symptoms.⁴⁸ Ifetroban, an oral TP-receptor antagonist, is undergoing investigation currently in patients with AERD (NCT03028350).

There is potential to modify a dysregulated arachidonic acid pathway through dietary intervention. Two prospective crossover trials on low salicylate diets demonstrated improvement in nasal symptoms and endoscopy scores, with one trial demonstrating improvement in asthma symptoms.^{49,50} Effects of fatty acid (FA) ingestion include inhibition of cellular 5-LO pathways and decreased uLTE₄,^{51,52} whereas omega-6 FA interferes with the anti-inflammatory effects of omega-3 FA.⁵³ One study showed that low omega-6, high omega-3 FA diet decreased uLTE₄, PGD metabolites, and nasal and asthma symptoms.⁵⁴

BIOLOGICS

Although there are no biological therapies specifically approved for AERD, there are medications with indications for both asthma and nasal polyposis. This allows for on-label use of all 5 biological therapies on the market for high-T₂ airway disease. Omalizumab is a recombinant antibody that binds to free IgE, thereby decreasing IgE density on mast cells and basophils. Omalizumab was initially approved for treatment of asthma, has demonstrated efficacy in AERD by decreasing symptoms during aspirin challenges.^{55–57} This effect may be related to the downregulation of high-affinity receptors on mast cells, resulting in decreased mast cell activation and mediator production, with lower uLTE₄ and PGD₂ metabolite levels.⁵⁸ A recent phase 3 study evaluating the effectiveness of omalizumab in CRSwNP has been completed, but results are not yet available (NCT03280537).

Mepolizumab is a humanized monoclonal antibody that binds free interleukin 5 (IL-5), preventing it from binding to its receptor on the surface of eosinophils. Mepolizumab has shown efficacy in patients with eosinophilic asthma^{59,60} and CRSwNP.⁶¹ Patients with AERD treated with mepolizumab for greater than 3 months showed

improvement in nasal congestion, anosmia, and asthma control.⁶² No comparator studies have been done with mepolizumab in AERD.

Reslizumab, which acts similarly to mepolizumab, is also approved for severe eosinophilic asthma. Treatment effect in patients with CRSwNP was evaluated in a post-hoc analysis of 2 asthma clinical trials. Patients with a history consistent with AERD had an 84% reduction in asthma exacerbations; sinus outcomes were not evaluated.⁶³

Benralizumab is a monoclonal antibody against the IL-5 receptor with a fucosylated modification that attracts natural killer cells to accelerate apoptosis. After administration, there is a dramatic decline in tissue eosinophils with nearly undetectable peripheral eosinophils.⁶⁴ Currently, benralizumab is approved for use in severe asthma with an eosinophilic phenotype but has not been specifically studied in AERD.

Dupilumab, a human monoclonal antibody that binds the alpha subunit of the IL-4 receptor, thereby blocking signaling of the Th2 cytokines IL-4 and IL-13, has been extensively studied in eosinophilic asthma, nasal polyposis, and atopic dermatitis.^{65,66} Approved for nasal polyposis in 2019, dupilumab has not been studied specifically in AERD. However, in a subgroup analysis of patients with AERD, improvement in polyp outcome was equivalent to all those with CRSwNP.⁶⁷

Biological therapies will likely be of enormous benefit to patients with AERD. Given the disease severity and highly eosinophilic nature of the disease, many patients with AERD qualify for biologic therapy. Whether a given biologic is superior or whether the magnitude of effect in AERD is similar to non-AERD patients merits further study.

UNIQUE EFFECTS OF ASPIRIN IN ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Aspirin is an effective treatment in AERD, but the exact mechanism of action related to this benefit is poorly understood. It is thought that NSAID reactions arise in part from a shunting of arachidonic acid down the leukotriene pathway, with COX-1 inhibition, leading to excess CysLT production and PGE2 depletion.

The Mechanism of Aspirin Benefit in Aspirin-Exacerbated Respiratory Disease

Aspirin desensitization is characterized by diminished airway LTE4 responsiveness and nasal mucosal CysLT1 receptor expression.^{20,21} This is likely secondary to a decrease in receptor-mediated signaling, as LTE4 is still produced at significant levels in patients with AERD on chronic aspirin therapy.^{3,68} The beneficial effects of aspirin desensitization may, in part, be mediated by IL-4 and STAT6, as aspirin and ketorolac can decrease IL-4 induced STAT6 expression.⁶⁹ Desensitization is characterized by a decrease in prostanoid metabolites (thromboxane, PGE2, and PGD2), which is consistent with the effects of aspirin COX-1 antagonism.³ There are increases in serum eosinophils and basophils with desensitization, possibly mediated by the chemokine receptor homologous molecule expressed on Th2 lymphocytes/D prostanoid 2 receptor (CRTH2/DP2) that causes PDG2-induced vasodilation and chemotaxis.^{3,70-72} Aspirin-induced decrease in PDG2 CRTH2/DP2 stimulation may play a role in the changes seen in desensitization, with decreased tissue recruitment of eosinophils and thereby increased peripheral eosinophils, as is seen in aspirin reactions and chronic therapy.³

CLINICAL TRIALS OF ASPIRIN THERAPY IN ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Aspirin therapy after desensitization (ATAD) is an effective treatment of upper and lower airway manifestations of AERD, with noticeable improvement as soon as 4 weeks after aspirin initiation^{73,74} (Table 1). After 6 months of treatment, a decrease

Table 1
Comparison of oral aspirin therapy after desensitization trials

	<u>Stevenson et al,⁸¹ 1984</u>	<u>Swierczynska-Krepa et al,⁸² 2014</u>	<u>Esmaeilzadeh et al,⁸³ 2015</u>	<u>Fruth et al,⁸⁴ 2013</u>
Study Type	Double-Blind Crossover	RDBPCT	RDBPCT	RCBPCT
Population	25 ATA	20 AIA, 14 ATA	34 CRSwNP, asthma, aspirin hypersensitivity	70 nasal polyps and CRS after sinus surgery, analgesic intolerance test >0.7
Duration	Two 3 month arms, 1 month washout	6 months	7 months	36 months
Aspirin dose	325 mg QD, 325 mg QID, 650 mg QID	624 mg QD	650 mg BID for 1 mo → 325 mg BID	100 mg QD
Definition of positive challenge	FEV1 decrease $\geq$ 25% compared with baseline	FEV1 decrease $\geq$ 20% compared with baseline	FEV1 decrease $\geq$ 20% compared with baseline or FEV1 decrease 15%–19% with nasoocular reaction/urticaria/angioedema	Not specified
Upper airway findings: aspirin vs placebo	- Decrease in nasal congestion and sinus pain - Trend but NS decrease in anosmia	- Decrease in SNOT-20, anosmia, sneeze, nasal blockade, and increase in peak nasal inspiratory flow - No change in sinus CT Lund-Mackay score	- Decrease in SNOT-22 - Decrease in sinus CT Lund-Mackay score	- Tendency but NS decrease in polyp relapse, anosmia - Later and less frequent polyp relapse on Kaplan-Meier curve - Improved nasal and paranasal quality of life and symptoms (nasal obstruction, postnasal drip, cephalgia, cough, sneeze, subjective olfaction)
Lower airway findings: aspirin vs placebo	- NS change in chest tightness, wheeze, cough, shortness of breath, chest congestion 48% had decrease in asthma symptoms	- Decrease ACQ - No change in FEV1, PEF	Increase in FEV1	Not measured

Effects on medication use: aspirin vs placebo	Decrease in nasal beclomethasone; no change in prednisone dose	- No change in asthma rescue medication use - Decrease in ICS dose	Trend but NS improvement in doctor-rated medication scores (significantly better in aspirin group after treatment compared with baseline)	Not measured
Other results	Tendency but NS improvement in upper and lower airway symptoms with increased aspirin dose	- Effects only seen in those with AIA on aspirin, not ATA on aspirin or placebo nor AIA on placebo - Higher baseline uLTE4 AIA vs ATA, increase only seen with aspirin challenge in AIA; no change with prolonged aspirin therapy - Increase in baseline 9α, 11β-PGF₂ AIA vs ATA, no change with aspirin challenge or prolonged therapy	- Placebo group had less severe disease (significantly lower SNOT-22 and Lund-Mackay scores) vs active group - NS change in eosinophils, IL-10, IFN-γ, and TGF-β in active vs placebo group after treatment	55.7% drop out rate (none due to medication side effects), no intention to treat analysis - Improved general health quality of life in aspirin group

Abbreviations: ACQ, asthma control; AIA, aspirin-intolerant asthma; ATA, aspirin-tolerant asthma; BID, twice daily; ICS, inhaled corticosteroid; NS, non-significant; PEF, peak expiratory flow; PGF₂, prostaglandin F₂; QD, daily; QID, four times daily; RDBPCT, randomized double-blind placebo-controlled trial; SNOT, Sino-nasal Outcome Test.

in the number of sinus infections, sinus/nasal and asthma symptoms and courses of oral steroids was observed, with sustained improvement seen at 1 year in one study.⁷⁵ In patients with AERD who are on aspirin treatment for greater than 1 year, there was a decrease in hospitalizations, upper respiratory infections, sinus surgeries, use of systemic and inhaled steroids, and nasal endoscopy scores along with an improved sense of smell and increased nasal inspiratory flow.^{76–78} In a group of 172 patients, 87% of those who were able to continue therapy for 1 year experienced improvement.⁷⁵ Re-operation is needed about every 3 years in AERD patients before desensitization, but aspirin therapy can decrease this to once every 10 years.^{76,77} Long-term studies have demonstrated no additional sinus surgeries in AERD patients on aspirin during follow-up periods ranging from 24 to 30 months post-desensitization, compared with 80% of non-desensitized AERD patients needing revision surgery at 24 months in one study.^{78–80} Desensitization has also been shown to improve alcohol tolerance in AERD.¹⁸

ASPIRIN-EXACERBATED RESPIRATORY DISEASE DIAGNOSIS

Aspirin challenge is the gold standard for AERD diagnosis, as there are no validated *in vitro* tests. uLTE4 is a promising AERD biomarker, but currently is not standardized for diagnostic purposes.³ Obtaining a history of either NSAID hypersensitivity or tolerance is not sufficient to diagnose AERD; in one study, 15% of asthmatics became aware of aspirin sensitivity only following challenge.⁸⁵ As NSAID sensitivity is acquired over time, history of symptoms with NSAID ingestion may not be present, especially in those who have avoided these medications. Alternatively, symptoms may be attributed to a flare in the underlying disease or to the condition that prompted ingestion (respiratory infection, menses) rather than the NSAID itself. Moreover, tolerance of low-dose aspirin does not exclude NSAID sensitivity, as demonstrated in a case series where 6 subjects on 81 mg aspirin daily had positive challenges after stopping aspirin for 10 days, with 5 of those subjects reacting to 81 mg or less.⁸⁶

Challenges are optimally performed before polypectomy to maximize diagnostic sensitivity, as 43% of patients who had pre-operative positive challenges were asymptomatic (silent challenge) with post-surgical challenge.^{1,32} Conversely, desensitizations are optimally performed 2 to 4 weeks post-polypectomy. There are several different desensitization protocols that have been published; the benefits and drawbacks to these various protocols have been outlined elsewhere.⁸⁷

DESENSITIZATION AND ASPIRIN MAINTENANCE THERAPY

Desensitization is often necessary, as non-aspirin therapies are often suboptimally effective, especially for preventing polyp regrowth and reducing symptoms and medication burden in AERD.^{45,78,88} It provides an alternative to NSAID avoidance and decreases the medication burden while improving symptoms compared with AERD patients not taking aspirin.⁷⁶

Maintenance of desensitization is accomplished via daily aspirin or other COX-1-blocking NSAID, but only aspirin has demonstrated efficacy in decreasing polyp regrowth and improving asthma and sinus symptoms. Re-sensitization occurs over a period of days after NSAIDs are discontinued, with partial (2–5 days) or complete (>5 days) repeat desensitization indicated depending on time from last dose.⁸⁹ Cross-desensitization to other NSAIDs is accomplished with at least 325 mg daily of aspirin or an equivalent dose of a COX-1 inhibitor, with perioperative ibuprofen bridging being done without adverse events or loss of desensitization.^{89–91}

The lowest dose of maintenance aspirin required for symptom improvement is not well-defined. In a series of 137 patients, about 50% were able to decrease their maintenance dose from 650 to 325 mg aspirin twice daily without recurrence of symptoms.⁹² Most patients have an increase in nasal congestion when the dose is less than 325 mg aspirin twice daily, although some studies have demonstrated efficacy when using 300 to 325 mg daily; lower doses (100 mg) may improve quality of life but do not decrease polyp regrowth.^{79,81,84,91,92}

ASPIRIN SIDE EFFECTS AND COMPLICATIONS OF THERAPY

In patients with AERD who are on adequate aspirin doses, a lack of response to desensitization and maintenance therapy indicates either misdiagnosis or nonresponse. Symptom improvement was seen in 78% after excluding those who stopped aspirin; of those patients who did not improve, most had uncontrolled comorbidities.⁷⁵ There are patients without identified comorbidities who still fail to demonstrate improvement. Ethnicity may play a role in aspirin response, as all those who failed to complete desensitization or improve in one study were African American or Latino.⁹³ Differences in underlying inflammation may also be contributing to a lack of response to aspirin therapy. The arachidonic acid metabolite 15-Hydroxyeicosate-traenoic acid was significantly higher at baseline and after 4 weeks of treatment in AERD patients who had improvement in asthma symptoms and FEV1 compared with patients who worsened with ATAD.^{32,93}

Failure to maintain desensitization, with NSAID-induced reactions occurring after an initial period of aspirin tolerance, is rare but has been reported.^{94,95} The mechanism has not been fully elucidated but may be similar to those patients who are not able to tolerate the desensitization process, with increased baseline PGD2 and thromboxane levels and a larger increase in PGD2 during desensitization.³

Side effects occurred in about 23.3% of patients in one study, and the rate of discontinuation is reported to be 3.5% to 14%.^{75,80,92} Gastrointestinal side effects are the most common, namely dyspepsia, gastrointestinal bleeding, and ulcers, although pancreatitis both during desensitization and maintenance therapy has been reported.^{92,96,97}

SUMMARY

AERD is an important phenotype of nasal polyposis. Given the paucity of pharmacologic studies on this condition, AERD seems to be still underappreciated. Patients with AERD have the highest rates of polyp recurrence, have more difficult-to-control asthma, and likely account for a disproportionate share of health care costs compared with their aspirin-tolerant peers. The role of ATAD merits ongoing study, and the future potential of biological therapy offers promise. Further mechanistic insights into the cause and propagation of this intensely type 2-mediated disease will continue to inform our understanding of nasal polyposis and severe asthma.

DISCLOSURE

Drs K. Luskin and H. Thakrar have nothing to disclose. Dr A. White has served on the speakers bureau for Regeneron/Sanofi and AstraZeneca; the advisory board for Optinose and ALK; the board of directors for WSAAI; and a primary investigator for Cumberland Therapeutics.

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