

Major complications of aspirin desensitization and maintenance therapy in aspirin-exacerbated respiratory disease

Auddie M. Sweis, MD¹, Tran B. Locke, MD¹ , Kevin I. Ig-Izevbekhai, BA¹, Theodore C. Lin, BS^{1,2} , Patrick K. Gleeson, MD¹, Alyssa M. Civantos, BA¹ , Ankur Kumar, BS¹, Andrew M. Corr, BA¹, Michael A. Kohanski, MD PhD¹ , James N. Palmer, MD¹, John V. Bosso, MD¹ and Nithin D. Adappa, MD¹

Background: Treatment of aspirin-exacerbated respiratory disease (AERD) includes endoscopic sinus surgery (ESS) and aspirin desensitization (AD) with aspirin therapy after desensitization (ATAD). The objective of this study was to determine the rate of major complications associated with aspirin use that resulted in the discontinuation of aspirin therapy.

Methods: This study was a retrospective chart review of patients with AERD who underwent ESS, AD, and ATAD at a single AERD tertiary center between July 2016 and February 2019. Complications associated with aspirin that resulted in the discontinuation of aspirin therapy were analyzed via analysis of variance and logistic regression.

Results: In total, 109 AERD patients underwent ESS with subsequent AD. Ten patients (9.2%) discontinued therapy after AD, before starting ATAD. Eight patients (7.3%) discontinued therapy after starting ATAD. There were 91 patients (83.5%) with no complications throughout ATAD. Reasons for discontinuation included gastritis, upper gastrointestinal (GI) bleed, anaphylaxis, persistent sinonasal symptoms, recurrent epistaxis, asthma exacerbation, and a nummular rash. There was no significant correlation between complication rate and (1) aspirin doses (analysis of

variance [ANOVA] F: 0.69; $p = 0.51$), (2) gender (odds ratio [OR] 0.56; 95% confidence interval [CI], 0.19 to 1.65; $p = 0.30$), (3) age (OR 1.04; 95% CI, 0.96 to 1.09; $p = 0.06$), or (4) race/ethnicity (OR 1.12; 95% CI, 0.88 to 1.44; $p = 0.36$).

Conclusion: AD with ATAD was associated with only a 0.92% incidence of a clinically significant GI bleed, and only a 0.92% incidence of anaphylaxis. A remaining 16 patients (14.7%) discontinued aspirin therapy due to minor clinical sequelae. These findings demonstrate that the majority of AERD patients tolerate AD with ATAD without any major complications. © 2020 ARS-AAOA, LLC.

Key Words:

chronic rhinosinusitis; medical therapy of chronic rhinosinusitis; eosinophilic rhinitis and nasal polyposis; asthma; therapeutics

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Aspirin-exacerbated respiratory disease (AERD), also referred to as Samter's triad or in Europe and the

Middle East as NSAID-exacerbated respiratory disease (NERD), is a progressive, acquired syndrome that is non-immunoglobulin E (IgE)-mediated. AERD consists of asthma, eosinophilic chronic rhinosinusitis with nasal polyposis (CRSwNP), and the development of respiratory reactions to cyclooxygenase 1 (COX-1) inhibitors. The peak onset of AERD occurs in the third and fourth decades of life.^{1,2} The condition is an aggressive inflammatory disorder of the sinuses and lower airways that progresses despite avoidance of aspirin/NSAIDs.³ Upper airway symptoms include nasal congestion, rhinorrhea, and sneezing, whereas lower airways symptoms include wheeze, shortness of breath, cough, and chest tightness. Patients may also experience gastrointestinal (GI) symptoms (ie, abdominal pain, nausea, or vomiting) and cutaneous symptoms

¹Department of Otorhinolaryngology, University of Pennsylvania, Philadelphia, PA; ²Lewis Katz School of Medicine, Temple University, Philadelphia, PA

Correspondence to: Nithin D. Adappa, MD, Department of Otorhinolaryngology, Hospital of the University of Pennsylvania, Perelman Center for Advance Medicine, 3400 Civic Center Blvd, 3 South, Philadelphia, PA 19104; e-mail: Nithin.adappa@pennmedicine.upenn.edu

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(ie, urticaria, rash, or angioedema). The consumption of alcoholic beverages also triggers upper and/or lower respiratory tract symptoms in 83% of AERD patients.

Treatment of this complex, aggressive, inflammatory disorder is multifaceted, including endoscopic sinus surgery (ESS) coupled with various medical therapies; eg, corticosteroids, leukotriene modifying agents (LTMAAs), aspirin desensitization (AD) with aspirin therapy after desensitization (ATAD), type 2 (T2) biologics, enhanced delivery systems for topical steroids (ie, exhalation delivery system with fluticasone [EDS-FLU]), and high-volume nasal steroid irrigations. Systemic corticosteroids, once the mainstay of AERD medical therapy, are fortunately being replaced by more tolerable treatments such as AD with ATAD, LTMAAs, or T2 biological therapies. Jerschow et al.⁴ completed a prospective study in which patients completed AD either before ESS or 3 to 4 weeks after ESS. The upper and lower airway reactions during desensitization were unanimously decreased in the group that underwent aspirin desensitization after ESS. In AERD patients who can tolerate it, AD with ATAD is the recommended adjunctive treatment following ESS. AD with ATAD is indicated in patients with: (1) persistent upper and lower airway symptoms despite appropriate medical therapy for asthma and appropriate medical and surgical therapy for CRSwNP; (2) AERD patients with comorbidities that would benefit from the use of aspirin and other NSAIDs (ie, patients with arthritis, coronary artery disease, etc.); (3) patients with AERD who require frequent bursts of systemic corticosteroids; and (4) patients with rapidly growing nasal polyps following ESS. AD with ATAD targets and suppresses the abnormal arachidonic acid metabolism that occurs in AERD patients, resulting in a tolerance to aspirin and other NSAIDs. This translates into reduced polyp growth.

Of all treatment options for AERD patients, the most robust data and the longest-studied therapy is AD with ATAD. At least 16 studies (4 double-blind placebo-controlled) over the past 3 decades have supported AD with ATAD as central to the management of AERD. The notable benefits gained from AD with ATAD as described must be weighed against the risks associated with long-term use of high-dose aspirin. To date, no study has formally analyzed the rate of major complications associated with AD and ATAD. The focus of our study was to identify the rate of aspirin-related complications that resulted in the discontinuation of aspirin therapy in AERD patients.

Patients and methods

This study was approved by the Institutional Review Board at the University of Pennsylvania. A retrospective review was performed at a tertiary academic medical center within the Division of Rhinology between July of 2016 and February of 2019. Inclusion criteria for the study consisted of (1) diagnosis of AERD; (2) bilateral ESS including maxillary antrostomy, total ethmoidectomy, sphenoidotomy, and frontal sinusotomy; (3) AD started approximately 6 weeks

TABLE 1. Baseline patient characteristics

Characteristic	Value
Total, n	109
Gender, n (%)	
Male	43 (39.4)
Female	66 (60.6)
Age (years), mean $\pm$ SD	51 $\pm$ 13
Race/ethnicity, n (%)	
Non-Hispanic	
White	88 (80.7)
Black	10 (9.2)
Asian	1 (0.92)
Hispanic/Latino	1 (0.92)
No response	9 (8.3)

SD = standard deviation.

after ESS; and (4) age $\geq$ 18 years. All patients underwent ESS by a rhinologist, and AD was performed by a single allergist/immunologist. The surgical and medical management of each patient was conducted at a single center, the Hospital of the University of Pennsylvania AERD Center. Exclusion criteria included (1) AERD patients who were noncompliant with ATAD; and (2) termination of ATAD in anticipation of elective surgery.

Outcome measures included aspirin doses during the maintenance period, clinical reactions patients reported during AD or ATAD, and the number of patients who discontinued aspirin therapy secondary to complications believed to be associated with aspirin use. The electronic medical record was reviewed for patient demographics (Table 1) including age, gender, race/ethnicity, and aspirin maintenance dose during ATAD.

AD was performed using a 2-day protocol. AD was always performed after complete ESS. Aspirin maintenance therapy during ATAD was based on the following protocol: initial dosing of 650 mg twice daily with titration after 3 to 6 months to a minimum of 325 mg daily based on patient response and tolerance.⁵ At 6 months post-AD, patients were usually on a stable daily aspirin maintenance dose of between 325 mg and 1300 mg. The prescribing physician at our institution adhered strictly to this protocol.

Statistical analysis was performed using Stata version 15.1 (StataCorp, College Station, TX). Parametric data were expressed as a mean. Comparisons were made using analysis of variance (ANOVA) or Student *t* test. Outcomes associated with binary and continuous variables were assessed using logistic regression.

TABLE 2. Complications of aspirin desensitization and aspirin therapy after desensitization that resulted in discontinuation of therapy

Complication	n (%)
Gastritis	9 (8.2)
GI bleed	1 (0.92)
Anaphylaxis	1 (0.92)
Exacerbation of upper airway symptoms	1 (0.92)
Recurrent epistaxis	1 (0.92)
Exacerbation of lower airway symptoms	4 (3.7)
Cutaneous reaction (nummular rash)	1 (0.92)

GI = gastrointestinal.

Results

After accounting for inclusion and exclusion criteria, 122 AERD patients from July 2016 to February 2019 were included in the study. Thirteen patients who completed AD were lost to follow-up. Of the remaining 109, 18 patients ultimately discontinued aspirin therapy (Table 2). Ten patients did not proceed with ATAD because of aspirin-related complications during AD. Eight patients who proceeded with ATAD later discontinued therapy because of aspirin-related complications. A total of 91 patients who completed AD went on to long-term ATAD without any aspirin-related complications; 61% ($n = 66$) were female and 39% ($n = 43$) were male. The age range was 22 to 76 years. The average age was 51 ± 13 years (mean $\pm$ standard deviation [SD]). Nine patients discontinued aspirin therapy because of stomach upset, diagnosed as gastritis. One patient on ATAD had a notable upper GI bleed resulting in termination of aspirin therapy. In this particular case, ATAD was discontinued and the patient received 1 unit of packed red blood cells. Moreover, on interval GI evaluation, there were no long-term sequela noted. This patient did not elect to restart aspirin therapy. One patient who was 1 week into ATAD, at an aspirin dose of 650 mg twice daily, suddenly developed a wheeze, diffuse skin rash, and a progressive globus sensation. The patient was successfully treated for anaphylaxis in the emergency room and made a complete recovery. The patient elected not to restart aspirin therapy. One patient was bothered by persistent to increased nasal congestion and terminated aspirin therapy. One patient had recurrent epistaxis and discontinued therapy. Four patients had an asthma exacerbation that resulted in termination of therapy. One patient had a cutaneous reaction (nummular rash) resulting in termination of aspirin therapy.

For all patients who went on to ATAD, the daily aspirin dose was either 325 mg daily, 650 mg daily, 975 mg daily, or 1300 mg daily. For patients taking 650 mg, patient doses were 325 mg twice daily. For patients taking 975 mg daily, patient doses were 325 mg in the morning and 650 mg in the evening or vice versa. For patients taking 1300 mg daily,

TABLE 3. Association between patient factors and presence of aspirin complications

Factor	Odds ratio (95% CI)	p
Race (Ref: white)	1.12 (0.88–1.44)	0.36
Sex (Ref: male)	0.56 (0.19–1.65)	0.30
Age	1.04 (0.96–1.09)	0.06
Factor	F statistic	p
Aspirin dose	0.69	0.51

CI = confidence interval.

patient doses were 650 mg twice daily. Length of follow-up ranged from 1 to 42 months, with the average follow-up duration being 16 ± 10 months.

Statistical analyses did not show any correlation between the dose of aspirin utilized during AD or ATAD (ie, 325 mg, 650 mg, 975 mg, or 1300 mg) and any of the complications associated with aspirin use (ANOVA: $F = 0.69$, $p = 0.51$). No statistically significant difference in complications was noted in females versus males (odds ratio [OR] 0.56; 95% confidence interval [CI], 0.19 to 1.65; $p = 0.30$). There was no statistically significant difference in age of patients with complications, vs those without (OR 1.04; 95% CI, 0.96 to 1.09; $p = 0.06$), or according to race/ethnicity (OR 1.12; 95% CI, 0.88 to 1.44; $p = 0.36$). These results are summarized in Table 3.

Discussion

This study shows that AD with ATAD offers a tolerable, easily manageable, and affordable treatment option for AERD patients, with low rates of complications. Walters et al.⁶ demonstrated that 85% of AERD patients who underwent AD with ATAD 10 years prior and were compliant with maintenance therapy reported persistent improvement in symptoms. Moreover, at 10 years out from desensitization, 62% of patients continued on with daily aspirin therapy because of the clinical benefit they reported. Only 38% discontinued daily aspirin for a variety of reasons (ie, lack of noticeable benefit, preparation for an upcoming surgery, or an adverse reaction to daily aspirin). Such findings have been corroborated by Berges-Gimeno et al.¹ In AERD patients, AD with ATAD has been shown to slow the rate of nasal polyposis recurrence and reduce the need for repeat sinus surgery, maintain 22-item Sino-Nasal Outcome Test (SNOT-22) improvements post-ESS, improve smell test scores, reduce oral corticosteroid usage, and decrease the number of antibiotic prescriptions needed.^{7,8} Additionally, AD with ATAD has been shown to improve tolerance to alcohol.⁹ The numerous benefits gleaned by AD with ATAD make it a worthwhile treatment regimen for patients with AERD.

Despite the numerous benefits of AD with ATAD, there is a paucity of data regarding the complications associated

with high-dose aspirin therapy used in AERD patients. More specifically, there have not been any studies to date detailing the rate of complications associated with aspirin use during AD and ATAD. Our study is the first to report on such outcomes. Of the 109 patients included in this study, 83% (n = 91) remained compliant with their therapy and did not complain of any clinically significant symptoms that could be objectively attributed to aspirin use. Of the 16.5% (n = 18) of patients who did discontinue their therapy, only 1 patient (0.92%) suffered from a GI bleed that required the immediate discontinuation of therapy. Similarly, only 1 patient (0.92%) suffered from anaphylaxis while on maintenance therapy during the first month of ATAD. In both cases, these patient were successfully treated with no long-term sequelae. Both patients elected not to restart aspirin therapy. The remaining 16 patients in the study had relatively minor reactions to AD with ATAD that ultimately resulted in their decision to discontinue treatment. It should be noted that there were AERD patients who continued on with ATAD despite having minimal side effects that could potentially be related to aspirin use. These side effects included mild GI upset, minor cutaneous reactions/rashes, mild bruising, and mild recurrent epistaxis. In these patients, symptoms were transient and short-lived. Because these mild symptoms can not definitively be attributed to aspirin use and because these patients continued on with ATAD, these complaints were not included in the complication rate; ie, the complication rate was determined by patient symptoms and signs that resulted in the discontinuation of aspirin therapy.

Rajan et al.¹⁰ performed a meta-analysis which demonstrated that the prevalence of AERD was 7.2% in the general population of patients with asthma. The prevalence of asthma in the United States is 19 million. Coupling these 2 data points, the estimated prevalence of AERD in the United States is 1,368,000. Further analysis demonstrated that the prevalence of AERD was 14.9% in patients with severe asthma, 9.7% in patients with nasal polyps, and 8.7% in patients with CRS.^{10,11} Therefore, it is quite clear that AERD is a rare disease process and understanding the risks of, benefits of, and alternatives to each of its treatment options (ie, ESS, AD with ATAD, T2 biologics, etc.) is critical because the physician and patient navigate the long-term treatment regimen together. For all patients in this study, only 1.83 % (n = 2) had a major complication that resulted in the discontinuation of aspirin therapy. The 2 complications were a major bleeding event and anaphylaxis, and both were readily reversible. With this AD with ATAD regimen, no patients suffered from permanent morbidity.

Patients should be made aware of these outcomes and how they compare to complications associated with other forms of AERD treatment; ie, therapy with T2 biologics. Moreover, when compared to other treatment options for AERD patients, AD with ATAD has been demonstrated to be economically cost effective.¹² The average annual cost for T2 biological therapy ranges from \$31,000 to \$39,000 per patient.¹³ In contrast, aspirin itself is quite inexpensive and this study shows that it comes with a low risk of major complications. AD with ATAD, following complete ESS, should be recommended as the mainstay of treatment for AERD patients who do not respond to topical corticosteroid and LTMA therapy, unless there exist relative or absolute contraindications.

Regardless of the low-risk profile of AD with ATAD that is shown in our study, there remains a subset of AERD patients in whom a relative or absolute contraindication to aspirin use exists. The use of aspirin doses larger than 81 mg daily in pregnancy notably increases the risk of bleeding to the patient and the fetus and may predispose to closure of the ductus arteriosus prematurely.¹⁴ Therefore, AD with ATAD is avoided during pregnancy.¹⁵ If a patient has a history of a coagulopathy or is taking an anticoagulant/antiplatelet agent, aspirin should likely be avoided. If a patient has a known prior history of peptic ulcer disease, then aspirin therapy is strongly contraindicated. If an AERD patient's asthma is poorly controlled, AD with ATAD should be delayed until symptoms are optimized so as to prevent further exacerbation of the patient's asthma. AERD patients with a history of eosinophilic esophagitis should avoid aspirin therapy because of the potential for exacerbation of gastrointestinal symptoms.¹⁶

Given the retrospective nature of our study, there are inherent limitations to our study design, including selection bias. To minimize this limitation, outcomes were focused on analyzing objective data only, such as the maintenance dose of aspirin therapy during ATAD, as well as the percentage of AERD patients who discontinued therapy following an aspirin-related complication.

Conclusion

In our study, AD with ATAD was associated with a 0.92% risk of a clinically significant GI bleed and only a 0.92% risk of anaphylaxis. Over 14 percent (14.7%) of patients in this study had less clinically significant complications that resulted in their decision to discontinue aspirin therapy. The majority of AERD patients in this study (83.5%) are able to tolerate AD with ATAD without any major complications. 

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