

Effectiveness of endoscopic sinus surgery and aspirin therapy in the management of aspirin-exacerbated respiratory disease

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ABSTRACT

Background: Aspirin therapy and/or type 2 (T2) biologics are used in the management of aspirin-exacerbated respiratory disease (AERD).

Objective: To identify the number of patients with AERD who tolerated aspirin therapy, yet due to persistent symptoms, incorporated T2 biologic management.

Methods: A retrospective review was performed between July 2016 and June 2019. Patients with AERD and who underwent endoscopic sinus surgery (ESS), aspirin desensitization (AD), and at least 6 months of aspirin therapy (ATAD) after AD, and who remained biologic-naïve up through this timepoint were included in the study. Introduction of a T2 biologic while on ATAD was the primary outcome. The secondary outcome was a change in a validated patient-reported outcome measure for chronic rhinosinusitis score between the postoperative predesensitization timepoint, and the 6-month postdesensitization timepoint, presented as means and compared by using the Student's t-test.

Results: A total of 103 patients met inclusion criteria. Two patients (1.9%) ultimately supplemented ATAD with a T2 biologic. The mean outcomes measure test score after 6 months of ATAD for patients who received biologics was 40.5 versus 15 in those who did not receive biologics ($p=0.02$). The mean differences between the postoperative predesensitization test score and the 6-month postdesensitization test score for patients who went on to receive biologics was an increase of 13 versus a decrease of 10 for those patients who did not receive biologics ($p=0.12$).

Conclusion: ESS, coupled with AD and ATAD, was successful in the long-term management of the majority of the patients with AERD, which rarely required the incorporation of T2 biologics. Patient questionnaires, such as outcomes measure test score, may identify aspirin therapy failures and help guide the practitioner in deciding when to introduce T2 biologics into the patient's treatment regimen.

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Aspirin-exacerbated respiratory disease (AERD) is a progressive, non-immunoglobulin E mediated syndrome that consists of asthma, eosinophilic chronic rhinosinusitis (CRS) 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 nonsteroidal anti-inflammatory drugs.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 symptoms (*i.e.*, abdominal pain, nausea, vomiting) and cutaneous symptoms (*i.e.*, urticaria, rash, or angioedema) after the ingestion of cyclooxygenase-1 (COX-1) inhibitors.

In general, the treatment for CRS is to begin with medical management, and patients with persistent symptoms may elect to undergo endoscopic sinus surgery (ESS).^{4,5} Some forms of CRS respond to medical therapy alone, whereas other forms of CRS require a combination of surgical and medical therapy. Beyond

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this, other phenotypes require a more personalized approach, depending on the underlying etiology. AERD is one particular CRS phenotype that is less responsive than other phenotypes to medical and/or surgical therapy. Treatment of AERD is multifaceted and includes ESS coupled with enhanced delivery systems for topical steroids and various systemic long-term medical therapies. Fortunately, long-term systemic corticosteroids, once the mainstay of AERD medical therapy, are being replaced by more tolerable, long-term medical therapies. The two key long-term medical therapies for patients with AERD include (1) aspirin desensitization (AD) with aspirin therapy (ATAD) and/or (2) type 2 (T2) biologics.

A common issue faced by medical and surgical subspecialists who manage AERD is in deciding whether to initiate (1) AD with ATAD or (2) T2 biologics. To date, no study has formally analyzed the percentage of patients with AERD who, despite tolerating AD with ATAD, ultimately go on to incorporate T2 biologic therapy into their treatment regimen. The focus of this study was to identify the percentage of patients who not only tolerated AD with ATAD but also those who elected to supplement or replace AT with T2 biologics because of persistent sinonasal concerns.

METHODS

This study was approved by the University of Pennsylvania Institutional Review Board. A retrospective review was performed at a tertiary academic medical center within the division of rhinology between July 2016 and June 2019. Inclusion criteria for the study consisted of (1) a diagnosis of AERD; (2) a bilateral complete ESS, including maxillary antrostomy, total ethmoidectomy, sphenoidotomy, and frontal sinusotomy; (3) being T2 biologic naive; (4) started AD 6–8 weeks after ESS; (5) on ATAD for at least 6 months; and (6) age $\geq$ 18 years old. All the patients underwent complete ESS by a fellowship trained rhinologist (DWK, JNP, NDA, MAK), and AD was performed by a single allergist/immunologist with extensive expertise in AERD. The surgical and medical management of each patient was conducted at an AERD center. Exclusion criteria included (1) patients with AERD who could not tolerate AD or ATAD, (2) patients with a history of biologic use before undergoing AD with ATAD, (3) patients who were noncompliant with ATAD, and (4) termination of ATAD in anticipation of elective surgery.

AD was performed by using the 2-day modified intranasal ketorolac/oral aspirin hybrid protocol.⁶ AD was always performed ~6–8 weeks 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

Table 1 Baseline patient characteristics (N = 103)

Characteristic	
Gender, n (%)	
Men	59 (57.3)
Women	44 (42.7)
Age, mean $\pm$ standard deviation, y	51 $\pm$ 11
Race or ethnicity, n (%)	
Non-Hispanic	
White	78 (75.7)
Black	10 (9.7)
Asian	1 (1.0)
Hispanic/Latino	3 (2.9)
Other	4 (3.9)
No response	7 (6.8)

minimum of 325 mg daily based on patient response and tolerance.⁷ At 6 months after AD, the 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. The introduction of a T2 biologic after at least 6 months of ATAD was selected as a primary outcome. The secondary outcome was the change in 22-item Sino-Nasal Outcome Test (SNOT-22)⁸ scores between the postoperative predesensitization timepoint and the 6-month postdesensitization timepoint. The electronic medical record was also reviewed for the type of T2 biologic initiated and patient demographics (Table 1), including age, gender, race and/or ethnicity.

RESULTS

A total of 184 AERD initially underwent AD. Three patients were excluded because they were started on a biologic after AD but before completing at least 6 months of ATAD. Nineteen patients were excluded because they could not tolerate ATAD for at least 6 months. None of these 19 patients during their care at our AERD center were transitioned to biologics. It is not known if these patients ultimately went on to receive biologics elsewhere. Fifteen patients were excluded for having a history of T2 biologic use before AD. Forty-four patients who tolerated AD with ATAD for 6 months were excluded because they did not have at least 1 year of follow up after AT was initiated. During their care at our AERD center, none of these 44 patients were on a biologic for as long as they were followed up. However, it is not known if any of these patients ultimately went on to receive biologics elsewhere.

After accounting for inclusion and exclusion criteria, 103 patients with AERD, from July 2016 to June 2019, were included in the study. Among the inclusion cohort, 42.7% (n = 44) were women and 57.3% (n = 59) were men. The age range was 24 to 77 years old, with a mean $\pm$

Table 2 Average 6-mo change in SNOT-22 score (postoperative predesensitization compared with the 6-mo postdesensitization) by race or ethnicity*

Race or Ethnicity	No. Patients	Change in SNOT-22, mean $\pm$ standard deviation	<i>p</i>
White	76	-8.222 $\pm$ 21.65	0.04
Black	10	-27.4 $\pm$ 21.34	0.16
Asian	1	-44 $\pm$ 0	—#
Hispanic/Latino	3	-17 $\pm$ 27	0.14

SNOT-22 = 22-Item Sino-Nasal Outcome Test.

*All these patients did not receive a type 2 biologic.

#No *p* value was reported because only one patient existed in this ethnic subgroup.

standard deviation age of 51 ± 11 years. After 6 months of ATAD, the length of follow up ranged from 12 to 42 months, with the mean $\pm$ standard deviation follow-up duration was 17 ± 11 months. Only two patients (1.9%) went on to receive T2 biologics after 6 months of ATAD. The mean SNOT-22 score after 6 months of ATAD for the two patients who ultimately went on to receive T2 biologics was 40.5 compared with 15 for patients who did not receive T2 biologics ($p = 0.02$).

The two patients who received T2 biologics had an average increase in SNOT-22 score of 13 when comparing the postoperative predesensitization SNOT-22 score with the 6-month postdesensitization SNOT-22 score. The remaining patients who did not receive T2 biologics saw an average decrease in the SNOT-22 score by 10 when comparing the postoperative predesensitization SNOT-22 score with the 6-month postdesensitization SNOT-22 score. In the patients who did

not receive T2 biologics, SNOT-22 score changes were assessed across all ethnicities (Table 2). Although the majority of patients in this study cohort were white, the improvement in SNOT-22 scores was maintained across all the ethnic groups. In addition, in a subscore analysis of SNOT-22 scores when focused specifically on decreased sense of smell and/or taste, the mean differences between the postoperative predesensitization score and the 6-month postdesensitization score in the group that received T2 biologic and the group that did not receive T2 biologic was an increase of 1 and a decrease of 0.429 ($p = 0.03$), respectively.

This outcome demonstrated the positive impact of long-term AT on this often difficult-to-treat symptom. Of the two patients who went on to receive T2 biologic therapy, one patient started dupilumab 17 months after AD with ATAD, and the other patient started mepolizumab 8 months after AD with ATAD. Neither

Table 3 Patients on AT alone vs patients on AT with a T2 biologic

		<i>p</i>
Patients with AERD and on ATAD, <i>n</i> (%)		
Added a T2 biologic	2 (1.9)	
Did not add a T2 biologic	101 (98.1)	
Average 6-mo SNOT-22 score change, mean $\pm$ SD*		0.12
Group that received a T2 biologic	+13 $\pm$ 39	
Group that did not receive a T2 biologic	-10 $\pm$ 20	
Mean SNOT-22 score after 6 mo of AT, mean $\pm$ SD		0.02
Group that received T2 biologic	40.5 $\pm$ 45.96	
Group that did not receive T2 biologic	15 $\pm$ 14	
Six-mo decreased sense of smell and/or taste, mean $\pm$ SD#		0.03
Group that received T2 biologic	+1 $\pm$ 1.41	
Group that not receive T2 biologic	-0.429 $\pm$ 1.89	

AT = Aspirin therapy; T2 = type 2; AERD = aspirin-exacerbated respiratory disease; ATAD = aspirin therapy after aspirin desensitization; SNOT-22 = 22-item Sino-Nasal Outcome Test; SD = standard deviation.

*Postoperative predesensitization SNOT-22 score compared with the 6-mo postdesensitization SNOT-22 score.

#Postoperative predesensitization compared with the 6-mo postdesensitization.

of these two patients discontinued ATAD. Both of these two patients were white. One hundred and one patients (98.1%) continued long term with ATAD without supplementing or replacing AT with a T2 biologic. These findings are summarized in Table 3.

DISCUSSION

This study demonstrated that patients with AERD who tolerate AD with ATAD rarely required the addition of further personalized medical management, *i.e.*, T2 biologics. Of the 103 patients with AERD who were on long-term AT in this study, only two incorporated a T2 biologic into their treatment regimen. Moreover, both patients continued with their long-term AT, despite adding a T2 biologic to their AERD treatment regimen. One patient saw a decrease in the SNOT-22 score, from 23 at postoperative predesensitization to 8 at 6 months (–15), and a SNOT-22 score of 6 at 12 months (–17), but, on subsequent nasal endoscopies, was noted to have mild polypoid disease and was started on dupilumab ~17 months after AD. The second patient saw an increase in the SNOT-22 score from 32 to 73 at 6 months after desensitization (+41) and was started on mepolizumab after ~8 months of AD with ATAD.

With regard to personalized medical management of the patients with AERD, the most robust data and the longest studied medical therapy for patients with AERD was related to AT, not T2 biologics. Four double-blind placebo controlled studies have supported AD with ATAD as central to the management of AERD.^{9–12} The long-term benefits of AT are clearly well documented in the literature. Walters *et al.*¹³ demonstrated that 85% of the patients with AERD who underwent AD with ATAD 10 years before and were compliant with maintenance therapy reported persistent improvement in symptoms.

Moreover, at 10 years out from desensitization, 62% of the patients continued with daily AT due to the clinical benefit they reported. Only 38% discontinued daily aspirin for a variety of reasons (*i.e.*, lack of noticeable benefit, preparation for an upcoming surgery, or an adverse reaction to daily aspirin).¹³ Such findings were corroborated by Berges-Gimeno *et al.*¹ In patients with AERD, AD with ATAD has been shown to slow the rate of nasal polyposis recurrence and reduce the need for repeated sinus surgery, maintain SNOT-22 improvements after ESS, improve smell scores, reduce oral corticosteroid usage, decrease the number of antibiotic prescriptions needed, and improve tolerance to alcohol.^{14–16}

The literature even goes on to specify that patients with AERD benefit most if ESS is completed first and AD with ATAD starts 6 to 8 weeks after ESS.^{15–17} In addition, Berges *et al.*¹⁸ demonstrated that significant clinical improvement may be observed as early as 4

weeks of AT. Nevertheless, because a lag time exists between starting AT and observing significant clinical improvement, we excluded three patients from this study because each had started his or her T2 biologic before completion of at least 6 months of AT. Overall, the numerous benefits gleaned from AD with ATAD make it a worthwhile treatment regimen for patients with AERD. Moreover, our current study highlighted that patients who tolerated AD with ATAD rarely needed to integrate T2 biologics into their treatment regimen.

Major complications associated with high-dose AT are rare. Sweis *et al.*¹⁹ showed that only 2 of a total of 109 patients (1.8%) experienced major complications that resulted in the discontinuation of ATAD. Despite the low-risk profile of AD with ATAD that has been demonstrated in the literature, there remains a subset of patients with AERD in whom a relative or absolute contraindication to aspirin use exists. The use of aspirin doses > 81 mg daily in pregnancy notably increases the risk of bleeding to the patient and the fetus, and may predispose to premature closure of the ductus arteriosus.²⁰ Therefore, AD with ATAD is avoided during pregnancy.²¹ Aspirin should also be avoided in patients with a history of coagulopathy, peptic ulcer disease, poorly controlled asthma, and/or eosinophilic esophagitis.²²

T2 biologics, as with AT, are also a form of personalized medical management for patients with AERD. Unlike AT, however, there is a paucity of data with regard to the use of T2 biologics in AERD. Hayashi *et al.*²³ performed a study of patients with AERD who completed 12 months of omalizumab treatment. The number of asthma exacerbations, daily doses of systemic steroids, and all asthma and nasal symptoms were significantly improved. However, this study was nonrandomized, noncontrolled, and only assessed 18 patients.²³ Tuttle *et al.*²⁴ studied patients with AERD who were treated with mepolizumab for at least 3 months. Although there were improvements in nasal congestion, anosmia, and asthma control, the study was retrospective and only included 14 patients.²⁴

Bachert *et al.*²⁵ performed two studies that assessed the efficacy of dupilumab in patients with uncontrolled CRSwNP. These were randomized, double-blinded, and placebo controlled studies. The two studies demonstrated that dupilumab resulted in improvements in nasal polyp scores (NPS), nasal congestion and obstruction scores, and Lund-Mackay scores.²⁵ Furthermore, Laidlaw *et al.*²⁶ performed a subanalysis of the patients with AERD within these studies, which demonstrated that dupilumab affords improved nasal polyp scores, asthma control, and lung function in this difficult-to-treat subgroup. Although the results are promising, they are limited by only 8 patients with AERD in the dupilumab-

treated group and only 11 patients with AERD in the placebo group.²⁶

In June 2019, dupilumab was approved by the U.S. Food and Drug Administration (FDA) for nasal polyposis. However, one must recognize that, regardless of this recent approval, dupilumab has had previous U.S. Food and Drug Administration approval for patients with asthma and/or atopic dermatitis. Given that many patients with nasal polyposis have comorbid asthma and/or atopic dermatitis, dupilumab is a medication that is not new to the population of patients with AERD. Although T2 biologics have been used for many years in patients with AERD, the majority of research on T2 biologics in CRS is limited to small randomized control trials and case series with limited follow-up durations.

Given the retrospective nature of our study, there were inherent limitations to our study design, including selection bias. To minimize this limitation, the outcomes were focused on analyzing objective data only, such as the percentage of patients with AERD and on AT who ultimately introduced T2 biologics into their treatment regimen. In addition, because dupilumab has only recently been approved for CRSwNP, there is the possibility that future studies may show that more patients will have T2 biologics added to their AERD treatment regimen than the 1.9% of patients in our study. Nevertheless, it is reassuring to note that 100% of patients in our study who tolerated AT did not discontinue AT even in the small number of cases in which a T2 biologic was added for persistent symptoms. For patients with AERD, the treating clinician must keep in mind that the literature is robust with regard to the efficacy and adverse effects of AT, although relatively limited with respect to the efficacy and adverse effects of T2 biologics.

CONCLUSION

In this study, ESS, coupled with AD and ATAD, is successful in the long-term management of the majority of patients with AERD, with very few patients needing to supplement this treatment regimen with T2 biologics. The majority of patients with AERD in this study were able to successfully manage symptoms with AT without T2 biologic treatment. Accordingly, we believe that first-line management of AERD should include ESS, followed by at least a 6-month trial of AD and ATAD,²⁷ whereas T2 biologics should be reserved for the minority subgroup with failure, intolerance, or a contraindication to AT. Furthermore, patient questionnaires, such as SNOT-22 scores, may identify AT failures and help guide the practitioner in deciding when to introduce T2 biologics into the patient's treatment regimen.

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