Safety and outcomes of aspirin desensitization for aspirin-exacerbated respiratory disease: A single-center study

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Background: Aspirin desensitization is an effective treatment option for aspirin-exacerbated respiratory disease. Aspirin desensitization protocol modifications have improved the safety and efficiency of this procedure, yet some providers remain reluctant to perform it.

Objective: The primary objective of this study was to evaluate the safety and outcomes of outpatient aspirin desensitization procedures. A secondary objective was to assess clinical characteristics that might predict reaction severity during aspirin desensitization.

Methods: Two hundred seventy-five patients underwent aspirin desensitization at Scripps Clinic between January 2009 and August 2015. Baseline patient characteristics and reaction results were analyzed in the 167 patients who reacted during desensitization.

Results: All of the 167 reactors, including 23 who were classified as severe reactors, were successfully desensitized in the outpatient setting. The average desensitization duration among reactors was 1.67 days, and the average duration for gastrointestinal reactors was 2.29 days. The mean baseline Sino-Nasal Outcome Test score was higher in severe reactors compared with nonsevere reactors ($P = .05$). Overall, patients receiving omalizumab had a similar reaction profile to those not receiving omalizumab.

Conclusions: Most patients undergoing aspirin desensitization will have symptoms. It remains difficult to predict the severity of these symptoms. However, desensitization can be done safely and efficiently in an appropriately equipped outpatient setting. This treatment option should be made available to all patients with aspirin-exacerbated respiratory disease. The Sino-Nasal Outcome Test score might be able to predict more severe reactions and merits further study. Eight of the 9 patients receiving omalizumab reacted during desensitization, suggesting that it does not block reactions during aspirin desensitization. (J Allergy Clin Immunol 2018;141:250-6.)

Key Words: *Aspirin-exacerbated respiratory disease, asthma, chronic rhinosinusitis, aspirin desensitization*

Aspirin-exacerbated respiratory disease (AERD) is characterized by chronic rhinosinusitis, nasal polyposis, asthma, and intolerance to COX-1–inhibiting medications.[1-3] The estimated prevalence among asthmatic patients is 7%, and the prevalence is even higher in patients with severe asthma and those with chronic rhinosinusitis and nasal polyps.[4] Patients with AERD experience various naso-ocular and/or lower airway symptoms after ingestion of COX-1–inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs). Less commonly, patients experience nausea, vomiting, abdominal pain, urticaria/angioedema, and, rarely, hypotension.

These adverse reactions to aspirin, other NSAIDs, or both are secondary to inhibition of COX-1 rather than an IgE-mediated phenomenon. The exact pathophysiology of AERD is not entirely understood but involves disruption of arachidonic acid metabolism, resulting in depletion of anti-inflammatory prostanoids, particularly prostaglandin E_2, and overproduction of proinflammatory cysteinyl leukotrienes. The ingestion of a COX-1 inhibitor exacerbates this dysregulation and causes a further reduction in levels of prostaglandin E_2, which normally functions as a "brake" mechanism on 5-lipoxygenase activity. This enhances type 2 inflammation through the actions of mast cells, eosinophils, platelets, and other mediators.[5-7]

Aspirin challenge is considered the gold standard for diagnosing AERD. Once the diagnosis is confirmed with a positive challenge result, management involves avoidance of all COX-1–inhibiting drugs or aspirin desensitization, followed by continuous aspirin therapy. Aspirin challenge and desensitization are usually done simultaneously in these patients, and aspirin desensitization will be used hereafter to refer to this combined procedure.

Aspirin desensitization is a provocative procedure and will likely induce symptoms in a patient with AERD. Therefore safety is an important consideration when performing aspirin desensitization in patients with AERD. Certain risk factors have been linked to severe bronchial reactions during aspirin desensitization, including no use of a leukotriene-modifying drug (LTMD) at the time of desensitization, baseline FEV_1 of less than 80% of predicted value, and a history of a prior emergency department visit for asthma.[8] Atopic status, sex, age at disease onset, systemic corticosteroid dependence, and the type or severity of the historical reaction to aspirin/NSAIDs have not been shown to be associated with severity.

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Abbreviations used
AERD: Aspirin-exacerbated respiratory disease
LTMD: Leukotriene-modifying drug
NSAID: Nonsteroidal anti-inflammatory drug
PNIF: Peak nasal inspiratory flow
SNOT-22: Sino-Nasal Outcome Test

Over the years, modifications to aspirin desensitization protocols have enhanced its safety. One of the best examples of this is the use of LTMDs, such as montelukast, for at least 1 week before aspirin desensitization.[9-11] LTMDs reduce the intensity of the reactions to aspirin, especially in the lower airways, but typically do not block the reactions completely, which is essential because one goal of desensitization is to confirm the diagnosis of AERD.[9-11] Another safety modification to the desensitization protocol was the addition of intranasal ketorolac before oral aspirin (Fig 1). The addition of intranasal ketorolac significantly reduces the mean percentage decrease in FEV_1 measurement, as well as decreasing the risk of extrapulmonary reactions, such as laryngospasm and gastrointestinal symptoms.[12]

Despite these modifications that have enhanced safety, a recent survey of aspirin desensitization practices among allergists and fellows in training in the United States indicated that only 62.5% of respondents perform aspirin desensitization for AERD.[13] Of those who do not, nearly 28% do not refer the patient to an allergist who does. Safety concerns, logistics of nursing care, and lack of exposure to the procedure during fellowship training were listed as the primary deterrents to use of desensitization in patients with AERD. This survey highlighted the need for more safety and outcomes data for aspirin desensitization in AERD.

Over the past decade, our group has successfully performed hundreds of outpatient aspirin desensitization procedures without any serious complications, hospitalizations, or deaths. As a result of this familiarity with aspirin desensitization, we sought to address some of the concerns highlighted in the survey and to supply readers with our outcomes and safety data by conducting a 5-year review of our aspirin desensitization procedures. Additionally, we analyzed various patient characteristics to determine which factors, if any, might influence or predict reaction severity.

METHODS

This was an institutional review board–approved review of all aspirin desensitization procedures performed at Scripps Clinic from January 2009 through August 2015. A total of 275 procedures were performed during that time period. Of those, 71 were excluded from chart review because of missing charts (n = 10), patients declining participation in research (n = 2), or use of an altered desensitization protocol (n = 59). This latter group included 3 patients who did not receive ketorolac per patient preference and 56 patients who participated in research projects that involved alterations of the standard desensitization protocol used at Scripps Clinic. The goal of the analysis was to gather information regarding outcomes of desensitization by using the specific protocol described in Fig 1. Therefore patients who did not undergo this protocol were excluded.

The charts of the remaining 204 patients were reviewed in detail. Of the 204 patients, 167 reacted during aspirin desensitization, and this group became the focus of our analysis.

Baseline patient characteristics, such as age, sex, ethnicity, medication use, FEV_1, and symptom scores, were reviewed. The reactors were then analyzed to assess the type and frequency of induced reactions, treatment provided, and changes in objective measures collected during the procedures. Basic statistical calculations were performed to determine whether any baseline characteristic was predictive of reaction severity during desensitization and to detect differences between reactions to nasal ketorolac and those to oral aspirin.

RESULTS

Patient demographics

Baseline patient characteristics for 167 reactors are presented in Table I. Mean age was 47.2 years, and there were nearly twice as many female as male patients. Mean baseline FEV_1 was 86% of predicted value (range, 37% to 114%). Mean peak nasal inspiratory flow (PNIF) rate was 155.7 L/min. The majority of patients (73.1%) had a history of positive skin test responses to inhalant allergens. Of those, 14.4% were receiving allergy immunotherapy at the time of desensitization. The average number of sinus surgeries was 2.9 (range, 0-12). Twenty-two (13.2%) patients had previously undergone at least 1 aspirin desensitization. The vast majority of patients (98.8%) were receiving an LTMD at the time of desensitization, with montelukast being the most common. Only 4.5% of patients were receiving omalizumab at the time of desensitization, whereas 26.3% were receiving systemic corticosteroids.

Symptom scores

Recently, we began collection of Asthma Control Test and Sino-Nasal Outcome Test (SNOT-22) scores before aspirin desensitization. Therefore only 45 patients had these baseline symptom scores measured during the above review period. Among these patients, the average Asthma Control Test score was 21.8 (range, 11-25); the average SNOT-22 score was 28.7 (range, 2-76).

Reaction characteristics

Table II contains data on reaction characteristics. The data are separated into 3 columns to define ketorolac reactors, aspirin reactors, and all reactors. Some patients reacted to both medications during the procedure and were included under both columns. More patients (88%) reacted to ketorolac than to aspirin (38.9%). Most ketorolac reactors (53.1%) reacted to the 7.58-mg dose, whereas most aspirin reactors (83.1%) reacted to one of the 60-mg doses.

Reaction types

Reactions were categorized as follows:

- *naso-ocular*—conjunctival injection, tearing, rhinorrhea, nasal congestion, sneezing, and pruritus;
- *classical*—naso-ocular symptoms and a 15% or greater decrease in FEV_1;
- *bronchial*—isolated decrease in FEV_1 of 15% or greater;
- *laryngeal*—symptoms involving the posterior oropharynx or larynx (ie, throat tightness)
- *gastrointestinal*—nausea, vomiting, gastric pain, or heartburn; and
- *cutaneous*—urticaria, angioedema, pruritus, or erythema.

Isolated naso-ocular reactions represented 56.5% of the reactions to nasal ketorolac, followed by classical (22.4%), mixed

Time	Dose
Day 1	
8:00 AM	1 spray ketorolac (1 spray in one nostril)
8:30 AM	2 sprays ketorolac (1 each nostril)
9:00 AM	4 sprays ketorolac (2 each nostril)
9:30 AM	6 sprays ketorolac (3 each nostril)
10:30 AM	60 mg aspirin
12:00 PM	60 mg aspirin
3:00 PM	DISCHARGE PATIENT
Day 2	
8:00 AM	150mg aspirin
11:00 AM	325 mg aspirin
2:00 PM	DISCHARGE PATIENT

To prepare nasal ketorolac:

1. Take ketorolac (60mg/2mL) and mix with preservative-free normal saline (2.75 mL).
2. Place combined solution in a nasal spray bottle (one that delivers 100 microliters/actuation).
3. Prime with 5 sprays before use, then each spray actuates 1.26 mg of ketorolac solution.
4. Patient should tilt head down while sprays and should sniff gently to avoid swallowing solution.

FIG 1. Nasal ketorolac and oral aspirin challenge protocol. After reactions are treated and resolve, continue the next scheduled ketorolac dose or repeat the oral provoking aspirin dose. Desensitization is complete after 325 mg of aspirin. The patient should take 650 mg of aspirin that evening and then continue 650 mg twice daily as their continuous aspirin dose until further instructed. If no reaction occurs within 3 hours after a 325-mg dose, consider it a negative challenge result.

(17.7%), and bronchial (2.7%) reactions. A single patient had an isolated laryngeal reaction to ketorolac. No isolated gastrointestinal reactions and no cutaneous reactions to ketorolac occurred. Isolated naso-ocular reactions were the most common reactions to aspirin as well, comprising 26.2% of the reactions. Classical (23.1%), bronchial (20.0), and mixed (17.0%) reactions were also common. Isolated laryngeal, gastrointestinal, and cutaneous reactions each occurred less than 5% of the time.

Several patients had mixed reactions, meaning they met the criteria for at least 2 of the categories described above. The most common mixed reaction among ketorolac reactors was naso-ocular combined with laryngeal. Among aspirin reactors, naso-ocular with bronchial, classical with gastrointestinal, and bronchial with laryngeal reactions were most common. Looking at all reactors, naso-ocular (43.1%), mixed (32.3%), or classical (18.6%) reactions occurred more than 90% of the time. Isolated bronchial, laryngeal, or cutaneous reactions were far less common. There were no isolated gastrointestinal reactions when all reactors were analyzed together.

Changes in PNIF and FEV_1

The mean decrease in PNIF was 32.4% and 23.0% in ketorolac and aspirin reactions, respectively ($P = .02$). On average, FEV_1 decreased by 11.0% (range, 0% to 63%) and 12.3% (range, 0% to 45%) in ketorolac and aspirin reactions, respectively, but this difference did not reach statistical significance ($P = .51$).

Treatments used during desensitization

Table III summarizes the treatments administered for reactions during aspirin desensitization. The reactors are divided into 3 columns to highlight treatments required for ketorolac reactors, aspirin reactors, and all reactors. Patients reacting to intranasal ketorolac required 3.1 treatments, on average, compared with 2.2 for those reacting to oral aspirin ($P = .01$). Considering all reactors together, the average treatment requirement per patient was 3.6.

Regarding ketorolac reactors, 74.8% received at least 1 antihistamine. Nasal decongestants (52.4%) and bronchodilators (40.8%) were also used frequently. Gastrointestinal medications were prescribed for 7.5% of all ketorolac reactors. A small percentage of ketorolac reactors required intramuscular epinephrine. Up to 15% of all ketorolac reactors did not receive any form of treatment despite having a documented reaction.

Aspirin reactors were most commonly treated with a bronchodilator (56.9%), followed by antihistamines (52.3%), nasal decongestants (18.5%), and gastrointestinal medications (10.8%). No aspirin reactor required intramuscular epinephrine, and 10.8% of aspirin reactors did not receive any treatment.

The final column in Table III looks at treatment frequency among all reactors. Overall, antihistamines were used in 76% of patients. Other commonly used medications were bronchodilators, nasal decongestants, and gastrointestinal medications. Overall, 21 (12.6%) patients did not require any form of treatment despite objective reactions.

Length of desensitization

The average length of desensitization among all reactors was 1.67 days (range, 1-4 days). Among those who had a gastrointestinal reaction, the average length of desensitization was 2.29 days (range, 1.5-4 days; $P = .006$).

Severe reactions

Twenty-three (13.8%) patients had severe reactions during desensitization. We defined a severe reactor as follows:

- required intramuscular epinephrine and/or
- required 3 or more doses of a β_2-agonist and/or had an FEV_1 decrease of 30% or greater.

TABLE I. Baseline patient characteristics

Age (y), mean (SD [range])	47.2 (11.7 [19-81])
Sex, no. (%)	
Male	63 (37.7)
Female	104 (62.3)
Ethnicity, no. (%)	
White	107 (64.1)
African American	3 (1.8)
Hispanic	6 (3.6)
Asian	1 (0.6)
Unknown	50 (29.9)
No. of sinus operations, mean (SD [range])	2.9 (2.2 [0-12])
Baseline FEV_1 (L), mean (SD [range])	2.89 (0.76 [1.25-5.27])
Baseline FEV_1 (% predicted), mean (SD [range])	86.0 (14.6 [37-114])
Baseline PNIF (L/min), mean (SD [range])	155.7 (49.9 [50-350])
Baseline ACT score*	21.8 (3.9 [11-25])
Baseline SNOT-22 score*	28.7 (21.0 [2-76])
Positive skin test response to aeroallergens, no. (%)	122 (73.1)
Active allergen immunotherapy, no. (%)	24 (14.4)
LTMD use, no. (%)	165 (98.8)
LTRA	
Montelukast	152 (91.0)
Zafirlukast	7 (4.2)
Zileuton	1 (0.6)
Zileuton and montelukast	5 (3.0)
Omalizumab use, no. (%)	8 (4.5)
Systemic corticosteroid use, no. (%)	44 (26.3)
Previous aspirin desensitization, no. (%)	22 (13.2)

ACT, Asthma Control Test; *LTRA*, leukotriene receptor antagonist.
*Forty-five patients had baseline SNOT-22 and ACT scores.

Four patients required intramuscular epinephrine, and 21 required 3 or more doses of a β_2-agonist and/or had an FEV_1 decrease of 30% or greater. Two of the patients requiring intramuscular epinephrine also met the other criterion. Table IV provides data for each patient requiring epinephrine administration during the desensitization. All 4 patients received epinephrine as treatment for ketorolac reactions.

Gastrointestinal reactors

Of the 17 patients who had a gastrointestinal reaction, 10 had the reaction to nasal ketorolac and 6 to oral aspirin, and a single patient had a gastrointestinal reaction to both ketorolac and aspirin. Eight (47%) of the 17 reported having had a historical gastrointestinal reaction upon aspirin or NSAID ingestion in the past.

Predictive risk factors

The final analysis performed attempted to identify whether any baseline characteristics were predictive of a severe reaction (Table V). Severe reactors, as defined above, were compared with those who did not have a severe reaction. Severe reactors had a higher mean baseline SNOT-22 score compared with nonsevere reactors ($P = .05$) and might be able to predict severe reactions, but only 45 of 167 participants had a baseline SNOT-22 score. Patients receiving systemic corticosteroids at the time of desensitization were more likely to have a severe reaction. The time interval between the most recent sinus surgery and aspirin desensitization was not found to be predictive of a severe reaction, and that time interval did not correlate with the patient's baseline SNOT-22 score.

Omalizumab use during desensitization

Eight (4.8%) of the 167 reactors were receiving omalizumab during aspirin desensitization. Of the 37 nonreactors, only 1 was receiving omalizumab therapy. Average baseline FEV_1 and PNIF values among these patients was 2.79 L and 85.4% of predicted value and 166.9 L/min, respectively. These measurements were comparable with those of the patients in this study who were not receiving omalizumab. However, the average number of sinus surgeries (5.1) before desensitization was higher in patients receiving omalizumab compared with all reactors (2.9). Fifty percent of the patients receiving omalizumab experienced a decrease in FEV_1 of 15% or greater. There was no difference in the number of treatments received for patients receiving omalizumab versus those not receiving anti-IgE therapy. The average length of desensitization was slightly higher in this subset of patients at 1.8 days compared with 1.67 days for all reactors. None of the patients receiving omalizumab were severe reactors.

DISCUSSION

Aspirin desensitization followed by daily aspirin treatment has long been regarded as an effective treatment modality in patients with AERD. Various safety measures have been implemented in aspirin desensitization protocols to mitigate the risks inherent in a provocative challenge. However, despite the efficacy and improved safety and efficiency of aspirin desensitization, a recent survey found that safety and logistical concerns deter many providers from using aspirin desensitization in the management of AERD.[13] Our current study helps to address these issues and also highlights other features relevant to aspirin desensitization in patients with AERD.

Using criteria consistent with higher severity of reactions, we found that nearly 14% of patients undergoing aspirin desensitization were classified as severe reactors. We also described 4 patients who received intramuscular epinephrine during desensitization. These patients were not hypotensive and did not demonstrate other findings suggestive of an anaphylactic reaction. Rather, it was the combination of symptoms (usually laryngospasm, gastrointestinal symptoms, or both) in light of the entire clinical course that prompted the supervising allergist to use epinephrine to more rapidly resolve the reaction. The percentage of severe reactions is a reminder that these procedures are not without risk and should be performed with proper precautions in place. Yet desensitization was successfully performed in an outpatient setting in 100% of the patients, including severe reactors.

It would certainly be helpful to accurately predict reaction severity based on baseline patient characteristics, but this proves to be difficult. A high SNOT-22 score might be predictive of reaction severity, but this finding requires further study given the smaller numbers of SNOT-22 scores that were collected during the review period. However, it is reasonable to conclude that patients with more active inflammation, particularly of the upper airway, are more likely to experience a significant reaction with COX-1 inhibition.

Despite previous findings by other authors,[8] we did not see a correlation between FEV_1 and reaction severity. This potential

TABLE II. Reaction characteristics for positive intranasal ketorolac and oral aspirin challenge results

Characteristic	Ketorolac reactor, n = 147 (88.0%)	Aspirin reactor, n = 65 (38.9%)	All reactors, n = 167
Most common provoking dose (mg)	7.58	60	NA
PNIF mean % decrease (SD [range])	32.4 (26.1 [0-100])*	23.0 (28.2 [0-100])*	29.5 (27.0 [0-100])
FEV_1 mean % decrease (SD [range])	11.0 (14.0 [0-63])†	12.3 (10.4 [0-45])†	11.4 (13.0 [0-63])
Type of reaction, no. (%)			
Naso-ocular	83 (56.5)	17 (26.2)	72 (43.1)
Classical	33 (22.4)	15 (23.1)	31 (18.6)
Bronchial	4 (2.7)	13 (20.0)	6 (3.6)
Laryngeal	1 (0.7)	2 (3.1)	2 (1.2)
Gastrointestinal‡	0 (0.0)	3 (4.6)	0 (0.0)
Cutaneous§	0 (0.0)	3 (4.6)	2 (1.2)
Mixed‖	26 (17.7)	11 (17.0)	54 (32.3)

NA, Not applicable.
*$P = .02$.
†$P = .51$.
‡Nausea, vomiting, gastric pain, or heartburn.
§Urticaria, angioedema, pruritus, or erythema.
‖Mixed reaction means the patient experienced a combination of reaction types.

TABLE III. Treatments used during reactions to intranasal ketorolac and aspirin challenges

Treatments received*	Ketorolac reactor, n = 147 (88.0%)	Aspirin reactor, n = 65 (38.9%)	All reactors, n = 167
Antihistamine, no. (%)	110 (74.8)	34 (52.3)	127 (76.0)
Oral/parenteral	106	33	124
Nasal	63	9	71
Ocular	17	4	21
Bronchodilator, no. (%)	60 (40.8)	37 (56.9)	85 (50.9)
β_2-Agonist	56	36	82
Racemic epinephrine	19	7	23
Nasal decongestant, no. (%)	77 (52.4)	12 (18.5)	84 (50.3)
Gastrointestinal, no. (%)	11 (7.5)	7 (10.8)	18 (10.8)
Antiemetic	5	5	9
Proton pump inhibitor	0	2	2
H2 blocker	8	4	12
Antacid	6	2	7
Misoprostol	3	1	4
LTMD, no. (%)	4 (2.7)	5 (7.7)	9 (5.4)
Systemic corticosteroid, no. (%)	8 (5.4)	2 (3.1)	10 (6.0)
Oral	3	1	4
Parenteral	5	1	6
Systemic epinephrine, no. (%)	4 (2.7)	0 (0)	4 (2.4)
Other, no. (%)	9 (6.1)	3 (4.6)	12 (7.2)
Intravenous fluids	4	2	6
Nasal saline	1	0	1
Nasal corticosteroid	2	0	2
Benzodiazepine	1	0	1
Viscous lidocaine	1	0	1
Acetaminophen	0	1	1
None, no. (%)	21 (14.3)	7 (10.8)	21 (12.6)
Total, mean (SD [range])	3.1 (2.5 [0-16])	2.2 (2.0 [0-11])	3.6 (2.4 [0-18])

H2, Histamine 2 receptor.
*Each patient might have received more than 1 type of medication within a medication class (eg, nasal and ocular antihistamines), and therefore the number of specific medications within each medication class will not necessarily add up to the number of patients treated with that medication class.

association might have been missed in our study because of the widespread use of LTMD drugs in our patients. The average baseline FEV_1 measurement among our patients was relatively high at 86% of predicted value, and nearly all were treated with an LTMD before and throughout desensitization, which has been shown to decrease bronchial reaction severity.[9-11] We also did not see a correlation between age and reaction severity, as seen in prior studies.[8,14] However, it is important to point out that the definition of a severe reaction is arbitrary and is not necessarily consistent across different studies.

This study addresses an important safety issue, which is the development of gastrointestinal symptoms during desensitization. In our experience gastrointestinal reactions during desensitization can be severe and frequently prolong desensitization. Half of the gastrointestinal reactors in our study had no reported historical gastrointestinal reaction to aspirin or

TABLE IV. Characteristics of those treated with intramuscular epinephrine during desensitization

Age, sex	LTMD	Systemic steroids	Baseline FEV_1 (% predicted)	Baseline nasal inspiratory flow	Reaction description	Decrease in nasal inspiratory flow (%)	Decrease in FEV_1 (%)
73, Male	Yes	Yes	89	100	Bronchial + severe laryngospasm	0	63
55, Male	Yes	No	82	70	Bronchial + severe gastrointestinal symptoms	14	7
55, Male	Yes	Yes	88	230	Classical + severe gastrointestinal symptoms	52	51
59, Female	Yes	Yes	85	110	Classical + severe laryngospasm	27	27

TABLE V. Reaction severity and baseline patient characteristics

Characteristic	No severe reaction	Severe reaction	*P* value*
Baseline SNOT-22 score, mean (SD)	26.1 (20.2)	42.7 (20.7)	.05
Baseline FEV_1, mean (SD)	2.9 (0.8)	2.9 (0.7)	.97
Baseline FEV_1 % predicted, mean (SD)	85.8 (14.9)	87.1 (12.1)	.70
Baseline PNIF, mean (SD)	155.3 (49.6)	158.2 (53.9)	.81
Baseline ACT score, mean (SD)	22.2 (3.7)	20.0 (4.7)	.18
Active allergen immunotherapy, no. (%)	23/144 (16.0)	1/22 (4.4)	.20
Systemic corticosteroid use, no. (%)	33/144 (22.9)	11/23 (47.8)	.01
No. of sinus operations, mean (SD)	3.0 (2.3)	2.1 (1.2)	.07
Atopy, no. (%)	105/140 (75.0)	17/23 (73.9)	.99
Age (y), no. (%)			
<30	10/144 (6.9)	1/23 (4.4)	.92
30-40	29/144 (20.1)	6/23 (26.1)	
>40	105/144 (72.9)	16/23 (69.6)	
Interval between sinus surgery and aspirin desensitization, no. (%)			
≤12 mo	81/133 (60.9)	12/19 (63.2)	.99
>12 mo	52/133 (39.1)	7/19 (36.8)	
Medications, no. (%)			
Zileuton	6/144 (4.2)	0/23 (0)	.41
Singulair	131/144 (91.0)	21/23 (91.3)	.99
Xolair	8/144 (5.6)	0/23 (0)	.60
Singulair + zileuton	5/144 (3.5)	0/23 (0)	.47
Zafirlukast	7/144 (4.9)	0/23 (0)	.35

ACT, Asthma Control Test.
*Fisher exact test (for proportions) or Wilcoxon rank sum test for (continuous variables).

other NSAIDs. Thus in this group of gastrointestinal reactors, a history of previous gastrointestinal reaction can predict a similar reaction during desensitization, but many patients will experience a gastrointestinal reaction for the first time during their desensitization. In our series 5.3% (9/167) had a gastrointestinal reaction in the absence of a history. This requires some degree of caution in terms of protocol choice. A rapid protocol can lead to administration of an additional dose of medication while a reaction is already progressing, which could lead to a more significant gastrointestinal reaction.

As mentioned previously, one of the other common deterrents to performing aspirin desensitization is logistics, including the time commitment required from both patients and providers. Balancing efficiency with safety is certainly an important consideration in aspirin desensitization. A recent publication by Chen et al[15] proposed an hourly dose-escalation protocol with an average desensitization length of 1.60 days in their 57 patients. This average included 9 patients who had a silent desensitization, which requires less time to perform. In our study patients required an average of 1.67 days to complete desensitization, and this number did not include any nonreactors. Furthermore, this number was reduced to an average of 1.60 days when excluding gastrointestinal reactors.

A faster protocol might be useful in some patients, but selecting which patients are appropriate candidates remains problematic. We did have a small percentage of patients (12.6%) with only mild reactions during desensitization and no need for treatment, which might make them suitable candidates for more rapid desensitization protocols. However, given the difficulty in predicting reaction severity and the possibility of dose stacking, the hourly dose-escalation protocol will need to be approached with caution.

Our study addresses another important topic in aspirin desensitization in patients with AERD, which is the role of omalizumab. A few case reports suggest a potential benefit of omalizumab use during aspirin desensitization. In a small total number of patients with AERD who received omalizumab treatment during aspirin desensitization, respiratory symptoms were significantly reduced or even absent after provocation with oral aspirin.[16-18] Omalizumab was discontinued in some of these patients, and subsequent aspirin challenges were able to elicit typical aspirin-provoked symptoms. A recent double-blind randomized trial of patients with AERD undergoing aspirin desensitization while receiving omalizumab also showed attenuation of aspirin-induced respiratory reactions compared with those receiving placebo.[19] These authors suggest that omalizumab might be able to restore aspirin tolerance without the need for aspirin desensitization. Yet if omalizumab can truly diminish the response to aspirin, it might introduce diagnostic uncertainty in those who do not react.

However, in our study we did not find any clear difference in reaction type or severity among those receiving omalizumab compared with those not receiving it during the time of aspirin desensitization. Furthermore, all 8 patients in our study had objective upper and/or lower airways reactions that did not appear to be blunted by the medication. Our data do not support the findings suggested by recent case reports. It is the authors' opinion that omalizumab remains an option for patients with AERD who are unable to complete aspirin desensitization or continue to have poorly controlled symptoms after desensitization. However, given the small number of patients receiving omalizumab in our study, more studies will need to be conducted to determine whether any true benefit can be obtained from using omalizumab during or in place of aspirin desensitization.

In summary, the safety and efficiency of in-office oral aspirin desensitization have improved and will likely continue to improve, thus making it a viable option for patients with AERD. The consistent theme of this and other studies of aspirin desensitization is that the reactions, even when more severe, are

able to be managed in an outpatient setting. There might be circumstances that make it difficult for individual offices to perform aspirin desensitization, but the opportunity to discuss this treatment option should be made available to each patient with AERD. Unfortunately, it is still difficult to predict who will have minimal symptoms and thus could be eligible for a faster dosing protocol or who will have more severe symptoms and require a multiday desensitization. Developing biomarkers or clinical scores to predict desensitization reactions are ideal targets for future study.

Clinical implications: Aspirin desensitization is a relatively safe procedure that can be performed in a properly equipped outpatient setting, and it is a treatment option that should be made available to all patients with AERD.

REFERENCES

1. Samter M, Beers RF Jr. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. Ann Intern Med 1968;68:975-83.
2. Szczeklik A, Nižankowska-Mogilnicka E, Sanak M. Hypersensitivity to aspirin and non-steroidal antiinflammatory drugs. In: Adkinson N Jr, Bochner B, Busse W, Holgate S, Lemanske R Jr, Simons F, ed. Middleton's allergy: principles and practice. 7th ed. Philadelphia: Elsevier; 2014:1227-43.
3. Stevenson DD. Aspirin and NSAID sensitivity. Immunol Allergy Clin North Am 2004;24:491-505.
4. 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;135:676-81.
5. Fischer AR, Rosenberg MA, Lilly CM, Callery JC, Rubin P, Cohn J, et al. Direct evidence for a role of the mast cell in the nasal response to aspirin in aspirin-sensitive asthma. J Allergy Clin Immunol 1994;94:1046-56.
6. Liu T, Laidlaw TM, Katz HR, Boyce JA. Prostaglandin E2 deficiency causes a phenotype of aspirin sensitivity that depends on platelets and cysteinyl leukotrienes. Proc Natl Acad Sci 2013;110:16987-92.
7. Choi JH, Kim JH, Park HS. Upper airways in aspirin-exacerbated respiratory disease. Curr Opin Allergy Clin Immunol 2015;15:21-6.
8. Hope AP, Woessner KA, Simon RA, Stevenson DD. Rational approach to aspirin dosing during oral challenges and desensitization of patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol 2009;123:406-10.
9. Dahlen B. Treatment of aspirin-intolerant asthma with antileukotrienes. Am J Respir Crit Care Med 2000;161(suppl):S137-41.
10. Berges-Gimeno MP, Simon RA, Stevenson DD. The effect of leukotriene-modifier drugs on aspirin-induced asthma and rhinitis reactions. Clin Exp Allergy 2002;32:1491-6.
11. White AA, Ludington E, Mehra P, Stevenson DD, Simon RA. Effect of leukotriene modifier drugs on the safety of oral aspirin challenges. Ann Allergy Asthma Immunol 2006;97:688-93.
12. Lee RU, White AA, Ding D, Dursun AB, Woessner KM, Simon RA, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol 2010;105:130.
13. 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;4:1253-5.
14. Dursun AB, Woessner KA, Simon RA, Durdu K, Stevenson DD. Predicting outcomes of oral aspirin challenges in patients with asthma, nasal polyps, and chronic sinusitis. Ann Allergy Asthma Immunol 2008;100:420-5.
15. Chen JR, Buchmiller BL, Khan DA. An hourly dose-escalation desensitization protocol for aspirin-exacerbated respiratory disease. J Allergy Clin Immunol Pract 2015;3:926.
16. Aksu K, Kurt E. Aspirin tolerance following omalizumab therapy in a patient with aspirin-exacerbated respiratory disease. Allergol Immunopathol (Madr) 2013;41:208-10.
17. Bobolea L, Barranco P, Fiandor A, Cabañas R, Quirce S. Omalizumab: a potential new therapeutic approach for aspirin-exacerbated respiratory disease. J Investig Allergol Clin Immunol 2010;20:448-9.
18. Bergmann KC, Zuberbier T, Church MK. Omalizumab in the treatment of aspirin-exacerbated respiratory disease. J Allergy Clin Immunol Pract 2015;3:459-60.
19. Lang DM, Aronica MA, Maierson E, Wang XF, Vasas DC, Hazen S. Omalizumab inhibits aspirin-provoked respiratory reaction in patients with aspirin exacerbated respiratory disease [abstract]. J Allergy Clin Immunol 2016;137(suppl):AB91.