Original Research

Long-term Clinical Outcomes of Aspirin Desensitization With Continuous Daily Aspirin Therapy in Aspirin-exacerbated Respiratory Disease

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Kristen M. Walters, MD[1], Jeremy D. Waldram, MD[1], Katharine M. Woessner, MD[1], and Andrew A. White, MD[1]

Abstract

Background: Aspirin-exacerbated respiratory disease (AERD), also known as Samter's triad or aspirin (ASA)-intolerant asthma, affects 7% of asthmatics and has a higher prevalence in those with chronic rhinosinusitis and concomitant nasal polyposis. ASA desensitization with daily ASA therapy is a uniquely beneficial treatment for this disease entity and has been shown to have a significant impact on symptom scores, polyp disease, and need for systemic corticosteroids. However, no long-term studies have demonstrated whether or not ASA therapy remains safe and beneficial for these patients beyond 5–10 years.

Objective: This study was designed to determine the clinical course of AERD patients desensitized between 1995 and 2010.

Methods: A 20-question survey was distributed to patients who successfully completed ASA desensitization between January 1995 and April 2010. The questions were designed to assess ASA safety and longitudinal effects of ASA therapy in AERD.

Results: Of the 285 patients contacted, 92 (32%) completed the questionnaire. Average length of follow-up was 15 years. Of survey responders, 35 patients had discontinued ASA therapy. Although adverse reactions occurred, many also discontinued due to lack of efficacy or need for surgery. For those remaining on ASA (62%), significant improvement in sense of smell, asthma, sinus, and allergic rhinitis scores were noted ($P \leq .001$). The majority of ASA patients (68%) had a positive response to treatment and did not require further sinus surgery. However, ASA therapy did not delay the time to next sinus/polyp surgery ($P = .27$) or reduce total number of sinus surgeries ($P = .56$) compared to those who stopped treatment. Nearly 85% of AERD patients on ASA therapy found it to be helpful in improving airway disease and quality of life.

Conclusion: Aspirin desensitization followed by daily maintenance ASA therapy appears to be safe and effective even after 10+ years of continuous use.

Keywords

aspirin-exacerbated respiratory disease, aspirin-intolerant asthma, nasal polyps, chronic rhinosinusitis, Samter's triad, aspirin desensitization, safety, NSAID intolerance, aspirin side effects, questionnaire, survey

Introduction

Aspirin-exacerbated respiratory disease (AERD) is defined as the clinical tetrad of chronic rhinosinusitis (CRS), eosinophilic nasal polyposis, asthma, and intolerance to cyclooxygenase-1 inhibiting drugs, such as aspirin (ASA) and ibuprofen, which can provoke adverse upper and/or lower airway symptoms upon ingestion.[1]

[1]Department of Allergy, Asthma and Immunology, Scripps Clinic, San Diego, California

Corresponding Author:
Kristen M. Walters, Department of Allergy, Asthma and Immunology, Scripps Clinic, San Diego, CA, USA.
Email: kwalters@rchsd.org

AERD often proves resistant to standard medical management, thus the important role of ASA as a unique treatment option for this patient group. In 1980, Stevenson et al. were the first to demonstrate the therapeutic benefits of ASA desensitization in the management of AERD, and it continues to be a highly successful treatment strategy for this population of patients.[2,3]

Numerous studies now confirm that ASA desensitization followed by daily ASA therapy results in improved nasal and global symptom scores, decreased need for systemic corticosteroids, sinus operations and hospitalizations, and also reduced rate of nasal polyp reformation.[3–8] The longest observation of ASA therapy in AERD by Berges-Gimeno et al. showed that the benefits of continuous ASA therapy started as early as 6 months and persisted for up to 5 years beyond the time of a patient's desensitization.[9]

Unfortunately, most outcomes data regarding ASA desensitization and therapy in AERD are limited by small numbers of AERD patients and a short follow-up period. To the best of our knowledge, no study has showed whether ASA desensitization continues to provide effective and meaningful disease control in AERD beyond 5 years. Furthermore, additional safety data are necessary in order to appropriately advise patients on long-term risk versus benefit.

The primary objective of this study was to determine the number of patients with AERD who had been desensitized and continued on ASA therapy for >10 years. Secondary objectives included determining the frequency of complications from chronic ASA therapy and assessing overall disease control as evidenced by rate of recurrent sinus infections and/or surgery, systemic corticosteroid use, emergency room (ER) visits, hospitalizations, and symptom scores both pre- and post-ASA desensitization.

Methods

A total of 609 patients underwent ASA challenge and desensitization at Scripps Clinic between January 1995 and April 2010. Of those, contact information was available for 285 patients through review of our electronic medical record (Allscripts), social media outlets, and other validated online information sources. A 20-question survey was generated and distributed to these individuals. Informed consent and permission to use data were granted based on voluntary completion of the study. The Human Subjects Committee of Scripps Clinic approved the study protocol.

Questionnaire Design

Patients were able to submit their questionnaire by mail or through an online survey site. All patients had the right to keep their responses anonymous. The following clinical outcomes were assessed:

Maintenance of ASA Therapy. Patients recorded whether they had continued or discontinued ASA therapy since the time of their initial desensitization. For those remaining on treatment, the average daily dose of ASA was collected. Reasons for temporary or permanent discontinuation with or without repeat desensitization were also documented.

Adverse Events. Any potential adverse event (AE) or side effect thought to be the result of chronic ASA therapy was noted, including whether or not ER or urgent care (UC) evaluation was required as a result of the event.

Number of Systemic Corticosteroid Bursts. The number of systemic corticosteroid treatments (oral and parenteral) required per year for treatment of an acute exacerbation of asthma, nasal/sinus symptoms, or both was recorded for both prior to and after ASA desensitization using the following ranges: 0–1, 2–3, 4–5, or >5.

Number of Daily Medications. The total number of daily medications used for AERD treatment was listed both before and after ASA desensitization. The following individual treatment classes were assessed: short-acting beta-agonist, inhaled corticosteroid, inhaled corticosteroids plus long-acting beta-agonist, nasal corticosteroid (NC), nasal antihistamine, leukotriene-modifying drug (LTMD), sinus rinse, decongestant (oral or topical), allergen immunotherapy, daily oral systemic corticosteroid, and omalizumab.

Number of Sinus Infections. A sinus infection was defined as an episode of purulent nasal discharge requiring treatment with antibiotics. The average number of sinus infections per year before and after ASA desensitization was marked using the following ranges: 0–1, 2–3, 4–5, or >5.

Number of Surgical Procedures. Surgical procedures included sinus debridement, nasal polyp resection, or both. The total number of surgical interventions performed was recorded before and after ASA desensitization.

ER or UC Evaluation for Asthma. The number of ER and/or UC visits per year for asthma evaluation and/or treatment was compiled before and after ASA desensitization using the following scale: never, 1–2, 3–4, or ≥5.

Hospital Admissions for Asthma. The number of hospital admissions for asthma per year before and after ASA desensitization was listed as follows: never, 1–2, 3–4, or ≥5.

Symptom Scores for Asthma and Nasal/Sinus/Allergy Control (Pre-/Post-ASA Desensitization). Subjective symptom scores for these measures were assessed using the following scale: 1, terrible; 2, poor; 3, fair; 4, good; and 5, excellent.

Symptom Scores for Sense of Smell (Pre-/Post-ASA Desensitization). Subjective symptom scores for sense of smell was obtained using the following scale: 0, no sense of smell; 1, intermittent partial sense of smell; 2, intermittent complete sense of smell; 3, partial sense of smell the majority of the time; 4, complete sense of smell the majority of the time; and 5, perfect and continuous sense of smell.

Global Assessment of ASA Desensitization and Treatment. A subjective score of the overall benefit of ASA desensitization for symptom control and personal well-being was recorded as follows: not at all helpful, slightly helpful, somewhat helpful, very helpful, and extremely helpful.

Statistical Analysis

Clinical measures pre- and post-ASA desensitization were compared using paired *t* tests. To ensure collected survey data were consistent and measurable, categorical variables were adjusted to numeric variables of the appropriate level (eg, score values of 0–1, 2–3, 4–5, and >5 or never, 1–2, 3–4, and ≥5 were transformed to 1 through 4, respectively). Similar conversions were performed for categorical responses assessing sense of smell, asthma symptom control, and sinus/nasal/allergy symptom control. Among patients who required sinus and/or nasal polyp surgery, a Mann–Whitney *U* test was conducted to determine whether ASA treatment affected the total number of surgeries and/or the length of time to the first surgery after desensitization. For all tests, *P* values are considered significant if less than .05. All statistical analyses were performed in R.

Results

Of the 285 patients who were contacted, 92 (32%) completed the questionnaire. Our survey response rate is comparable to those previously reported.[10] Over half (55%) of the respondents were female with an average age of 61.7 years (range: 28–86 years). ASA desensitizations occurred between 1981 and 2010 with 84% of the respondents having undergone desensitization more than 10 years from the time the survey was generated. Over 50% of the patients (49 of the 92) completed the procedure between the years 2000–2005.

Survey responses were immediately sorted into 2 groups based whether or not the patient was actively on daily ASA therapy. Based on earlier findings by Berges-Gimeno et al., patients who had been desensitized and on daily ASA therapy for less than 6 months were excluded from final analyses, as they would not have been considered to be on long-term ASA (n = 15).[9]

Maintenance of ASA Therapy and AEs

Of all survey responders, 57 (62%) currently remain on daily ASA therapy as compared to 35 (38%) who have since discontinued ASA therapy (Table 1).

In regard to the latter, ASA therapy was discontinued an average of 8.3 years following their initial desensitization (range: 0–30 years). Fifteen of these patients were on ASA therapy for less than 6 months. The most common reason for discontinuing ASA was the development of adverse side effects which included both gastrointestinal (*stomach upset, acid reflux, peptic ulcer disease*) and/or hematologic (*easy bruising/bleeding*) reactions. Of those reporting adverse reactions, only 3 patients required ER or UC evaluation as a result of their symptoms. There were no hospitalizations. Other frequently reported reasons for ASA discontinuation included lack of clinical benefit (26%) and need for surgical intervention (23%).

Of the survey respondents remaining on active ASA treatment, over 70% are maintained on a total daily

Table 1. Rate of ASA Continuation and AEs Following ASA-desensitization.

Total number of responses	**92**
Discontinued ASA treatment, no. (%)	**35 (38)**
Average years postdesensitization, no. (range)	8.3 (0–30)
Reasons for discontinuation, no. (%)	
Adverse reactions	**13 (37)**
Lack of clinical benefit	**9 (26)**
Need for antiplatelet/antithrombotic medication	2 (6)
Surgical procedures	**8 (23)**
Physician recommendation	1 (3)
Financial constraints	1 (3)
Unknown	1 (3)
Total ER/UC visits for AE	3
Remaining on ASA treatment, no. (%)	**57 (62)**
Maintained on total doses between 325 and 650 mg/day	41 (72)
Underwent additional ASA desensitization	18 (32)
Adverse side effects	12 (21)
Gastrointestinal	7
Hematologic (easy bruising/bleeding)	5
Total ER/UC visits for AE	1

Abbreviations: AE, adverse events; ASA, aspirin; ER, emergency room; UC, urgent care.

dose of ASA between 325 and 650 mg (range: 40.5–1300 mg/day). Gastrointestinal and/or hematologic side effects were reported by 21% of the patients and only 1 required an ER/UC visit for their reaction (*prolonged bleeding after a fall*).

Approximately one-third of the patients underwent repeat ASA desensitization at some time point following their first desensitization. Of those, 14 of the 18 (78%) patients were performed as a result of ASA discontinuation (≥72 h) required for an elective surgical procedure or pregnancy.

Of note, no difference was seen among those continuing versus discontinuing ASA therapy in regard to age, sex, ethnicity, or age at the time of their initial desensitization.

Medication Analysis

Figure 1(a) and (b) shows a comparison of medications (listed by drug class) across survey responders who remain on ASA therapy versus those who have discontinued ASA, respectively.

The majority of patients, *regardless of their ASA status*, showed no change and were continued on daily controller medications following desensitization: inhaled corticosteroids, LTMDs, and topical NC therapy.

There was a generalized trend toward mean reduction in total number of daily medication requirement following ASA desensitization in those who remained on ASA therapy. Active ASA users, on average, reported the use of 5.2 total medications/day prior to ASA desensitization (range: 1–9; standard deviation (*SD*): 1.88) which decreased to 4.4 medications/day (range: 2–9; *SD*: 1.65) postdesensitization ($P = .008$; Table 2).

A significant reduction in the number of systemic corticosteroid bursts required per year was seen in patients who remained on ASA therapy ($P \leq .001$) (Table 2). Moreover, 64.3% of the current ASA users were able to completely discontinue daily systemic steroid therapy following desensitization. In comparison, only 40% of the patients who stopped ASA were able to reduce or discontinue their systemic corticosteroid dependence.

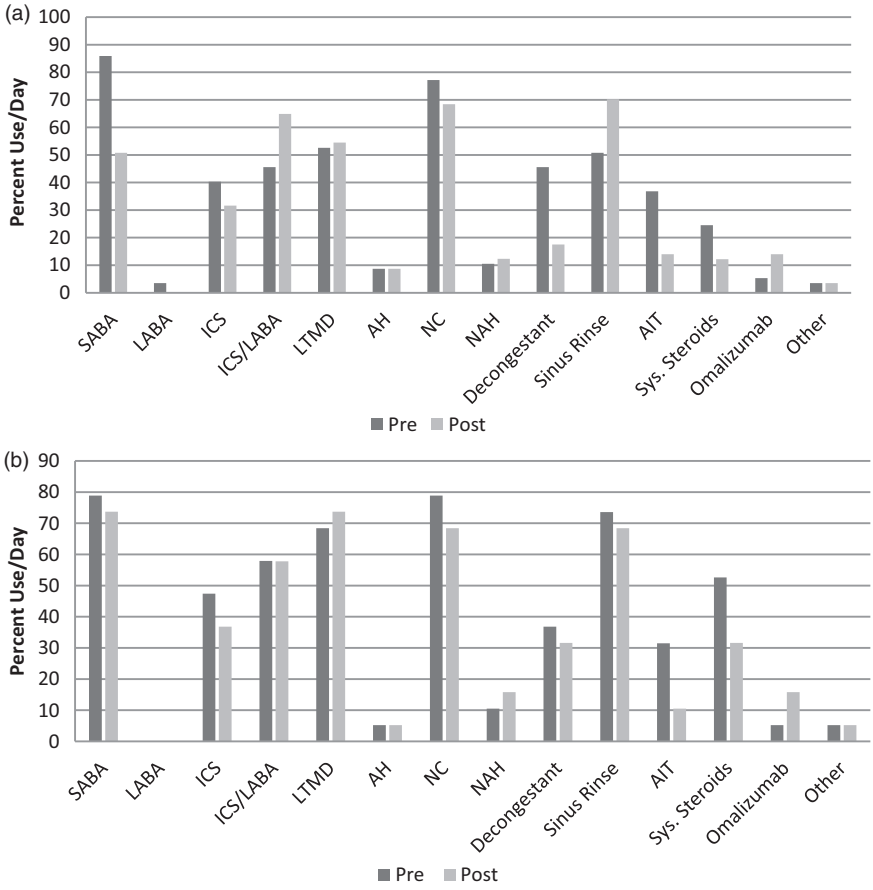

Figure 1. (a) Daily medication use in AERD patients on continuous daily ASA therapy, pre-and post-ASA desensitization. (b) Daily medication use in AERD patients not on ASA therapy, pre- and post-ASA desensitization. AH, antihistamine (oral); AIT, allergen immunotherapy; ICS, inhaled corticosteroid; ICS/LABA, inhaled corticosteroid with long-acting beta-agonist; LABA, long-acting beta-agonist; LTMD, leukotriene-modifying drug; NAH, nasal antihistamine; NC, nasal corticosteroid; SABA, short-acting beta-agonist; Sys, systemic.

Table 2. Clinical Characteristics and Symptom Scores in Active ASA Users (Pre- and Post-ASA Desensitization)

	Predesensitization		Postdesensitization		Δ	
	Mean	*SD*	Mean	*SD*	Mean	*P* Value
Medications/day	5.23	1.88	4.45	1.65	−0.76	.008
Steroid bursts/year[a]	2.31	1.05	1.41	0.77	−0.91	<.001
Sinus infections/year[a]	2.48	0.94	1.41	0.72	−1.05	<.001
UC/ER visits/year[b]	0.81	0.96	0.25	0.49	−0.55	<.001
Hospitalizations/year[b]	1.48	0.75	1.10	0.35	−0.38	<.001
Sense of smell	0.66	1.06	1.74	1.65	+1.08	<.001
Asthma scores	2.68	1.10	4.09	0.79	+1.41	<.001
Sinus/AR scores	1.76	0.89	3.66	1.06	+1.90	<.001

Abbreviations: AR, allergic rhinitis; ER, emergency room; *SD*, standard deviation; UC, urgent care.
[a]For analysis purposes, scores of 0–1, 2–3, 4–5, and >5 were transformed into levels 1, 2, 3, and 4, respectively.
[b]For analysis purposes, scores of never, 1–2, 3–4, and >4 were transformed into levels 1, 2, 3, and 4, respectively.

Markers of Clinical Disease

Table 2 shows a comparison of various clinical markers and symptom scores, both pre- and post-ASA desensitization, in those who remained on daily ASA therapy. All comparisons were statistically significant with the highest average change (Δ) seen in regard to overall control of rhinosinusitis symptoms.

Of those actively maintained on ASA therapy, 32% (18 of the 57) of the patients have undergone at least 1 sinus and/or nasal polyp surgery since the time of their desensitization as compared to 79% (15 of the 19) of the patients who discontinued ASA. In both groups, nasal polypectomy was most commonly performed.

However, no difference was seen in regard to the *total number* of sinus surgeries required in either ASA or non-ASA users with an average number of 1.66 versus 2.01 total procedures, respectively ($P = .56$). In addition, continuous ASA therapy did not delay the length of time between desensitization and the first sinus and/or polyp surgery following the procedure ($P = .27$).

This suggests that there are "responders" and "nonresponders" of rhinosinusitis with daily ASA management. Although the majority of patients (68%) who continued ASA therapy did not need further surgical correction of their sinus disease, the "nonresponders" showed equivalent clinical outcomes to those patients who had previously discontinued ASA.

Global Assessment of ASA Desensitization and Treatment

Nearly 85% of the AERD patients remaining on continuous daily ASA therapy have found ASA desensitization and treatment to be very or extremely helpful in controlling their upper and/or lower airways disease and general quality of life (Table 3). The vast majority (73%) of patients who discontinued ASA also reported that ASA desensitization was at least somewhat effective in improving their symptoms.

Table 3. Global Assessment of ASA Desensitization and Treatment in Current ASA and Non-ASA Users.

	Extremely Helpful	Very Helpful	Somewhat Helpful	Slightly Helpful	Not At All Helpful
ASA, no. (%)	30 (52)	18 (32)	5 (9)	4 (7)	0 (0)
Non-ASA, no. (%)	5 (26)	5 (26)	4 (21)	1 (5)	4 (21)

Abbreviation: ASA, aspirin.

Alcohol Intolerance

A recent study showed that alcohol-induced airway reactions are significantly more common in the AERD population as compared to ASA-tolerant controls.[11] Of our survey responders, 60.5% of the patients reported intolerance to alcohol, which included varying degrees of nasal-ocular reactions and/or bronchospasm. Of these, 37% identified that ASA desensitization improved their ability to tolerate alcohol ingestion.

Discussion

To the best of our knowledge, this is the first study to address long-term safety, tolerability, and the overall impact of chronic ASA management in AERD patients who have been maintained on daily ASA therapy for a minimum of 10 years or more.

In those who remained on daily ASA therapy, we combined objective measurements and patient self-assessment scores and found improvement in sinus and asthma symptoms controls as well as a significant reduction in annual sinus infections, ER visits and/or hospitalizations for asthma, and oral corticosteroid requirements (Table 2). Nearly 85% of the patients feel

that ASA desensitization and treatment have been "very helpful" or "extremely helpful" in controlling disease and overall quality of life (Table 3).

In this study, 32% of the active ASA patients versus 79% of the non-ASA patients had required at least 1 sinus and/or nasal polyp surgery since the time of their desensitization. Although ASA did not delay the length of time between desensitization and the next sinus or polyp surgery ($P = 0.27$), these data suggest that ASA therapy essentially halts the formation of polyps in a certain "responder" subgroup of AERD patients.

Of the 107 survey respondents, 15 noted that they took ASA for <6 months. These subjects were not specifically queried about their reasons for discontinuation, but this likely mirrors the data from Berges-Gimeno et al. which reported over an initial 5-year observation that 13% stopped ASA due to gastrointestinal upset, urticaria, or bleeding/bruising. Another 11% did not obtain benefit and discontinued in their study.[9,12] It appears that over a longer observation period, up to 38% of the survey responders eventually discontinued ASA therapy following their desensitization. Adverse side effects (gastrointestinal or hematologic) were the reason for discontinuing ASA treatment in only one-third of the patients (13/35). Despite these adverse reactions, only 3 patients required urgent evaluation. None of these urgent visits led to hospitalization or death. Half of the group that discontinued ASA did so due to either a surgical procedure (8 of the 35) or lack of clinical benefit (9 of the 35). Overall, the majority of AERD patients on ASA did quite well, and only 14% (13 of the 92) of the patients in our study discontinued ASA due to adverse effects. This intolerance rate is not significantly different than when ASA is used at lower doses (75–325 mg) for cardiovascular indications.[13] A recent study showed concern for renal safety as a result of decreased urinary creatinine following long-term treatment with ASA after desensitization, but this requires further study.[14] No report of kidney injury was reported in this study.

It is clear that this survey-based study is subjected to several types of inherent bias which can affect the strength of interpretation of certain data. Ideally, future studies could consider correlating measurements of urinary metabolites (ie, PGD_2 and LTE_4) with patient-reported information to reinforce study outcomes.[15] Despite these limitations, the themes that emerge from this study are relatively consistent with published conclusions from other studies of ASA therapy in AERD. Our study has the advantage of extending these findings to a longer follow-up period (≥10 years). We continue to recommend that AERD patients with recalcitrant upper and/or lower airways disease (despite optimal medical therapy) be considered for ASA desensitization and receive a trial of daily ASA as add-on treatment. This is especially true for those who have aggressive CRS and nasal polyposis given a recognized decrease in the need for future surgical intervention in ASA responders.

Given new biologic therapies which are also emerging for the treatment of eosinophilic CRS and nasal polyposis (as well as severe asthma), it will be necessary to study these pharmacologic interventions within the AERD population.[16] Furthermore, it would be ideal to have readily accessible biomarkers to identify patient phenotypes and determine the therapeutic approach to which they would best respond.[16] Until then, our long-term data show that chronic ASA therapy is relatively safe with low risk for severe adverse side effects; however, given known limitations with questionnaire-based studies, this study also highlights the need for future prospective studies detailing these events.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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