

Meta-analysis Exploring Sinopulmonary Outcomes of Aspirin Desensitization in Aspirin-Exacerbated Respiratory Disease

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Abstract

Objective. The objective of this study is to explore the sinopulmonary outcomes of aspirin desensitization through a systematic review and meta-analysis.

Data Sources. Embase and OVID Medline databases.

Review Methods. A systematic review of published articles on outcomes following aspirin desensitization in any language for relevant articles was performed in February 2019. Outcomes included sinonasal quality-of-life assessment, sense-of-smell scores, FEV-1 (forced expiratory volume in 1 second), and medication/steroid use.

Results. Thirteen studies met the inclusion criteria out of 6055 articles screened. Aspirin desensitization resulted in significant improvement in FEV-1 and reduction in asthma medication/steroid use ($P < .05$). There was no significant improvement in the sinonasal quality of life of patients who underwent aspirin desensitization ($P = .098$).

Conclusion. Aspirin desensitization appears to be effective in improving pulmonary outcomes and should be considered in the treatment of patients with aspirin-exacerbated respiratory disease. However, good-quality studies are still needed to determine the ideal protocol tailored to individual patients.

Keywords

aspirin-induced asthma, aspirin-tolerant asthma, oral aspirin desensitization, acetylsalicylic acid, ATA (aspirin-tolerant asthma), NSAID, nonsteroidal anti-inflammatory drug, SNOT-22, Sino-Nasal Outcome Test), immunologic, humans, respiration disorders, Samter's triad, AERD

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Aspirin-exacerbated respiratory disease (AERD) is a condition characterized by a tetrad of chronic rhinosinusitis, nasal polyposis, asthma, and aspirin sensitivity. When compared with patients with aspirin-tolerant chronic sinusitis, patients with AERD undergo 10-times more sinus surgery.¹ Diagnosis of AERD is based on a positive clinical history of rhinosinusitis, nasal polyposis, and

worsening of respiratory symptoms with exposure to aspirin or other NSAIDs (nonsteroidal anti-inflammatory drugs). In the United States, >1.3 million people are affected by this disease.² Treatment entails a combination of optimal medical therapy for chronic rhinosinusitis, asthma symptom control, endoscopic sinus surgery, and aspirin desensitization. The cost of AERD is a function of the combined expenditures of the individual components of the tetrad with the cumulative effect of chronic disease. Historically, aspirin desensitization originated with the discovery of aspirin sensitivity in a subset of patients with asthma. It was later discovered that patients could become desensitized in the late 1970s and early 1980s, shortly after AERD became a distinct diagnosis. Stevenson et al³ published a case report describing 2 patients with a history of positive oral aspirin challenges who were subsequently treated with daily aspirin desensitization regimens. Their aspirin doses were escalated from 325 mg to 650 mg, resulting in drastic improvements in their clinical course. Since then, several studies have shown improvements in quality of life, nasal polyp burden, and need for surgical intervention as a result of aspirin desensitization.

The aspirin desensitization protocol has evolved over the years to optimize results and minimize patient inconvenience. There have been several protocols implemented by various institutions but no standardized approach to these protocols. Initially, desensitization protocols lasted from 3 to 7 days,^{4,5} but currently these can be completed in as little as 9.5 hours.⁶ Historically, desensitization was performed in an inpatient setting and occasionally in the intensive care unit,⁷ but more recently, emphasis has been placed on outpatient protocols. With protocols shifting to outpatient settings, research institutions have been able to accelerate the desensitization process while maintaining patient safety.⁵ A typical

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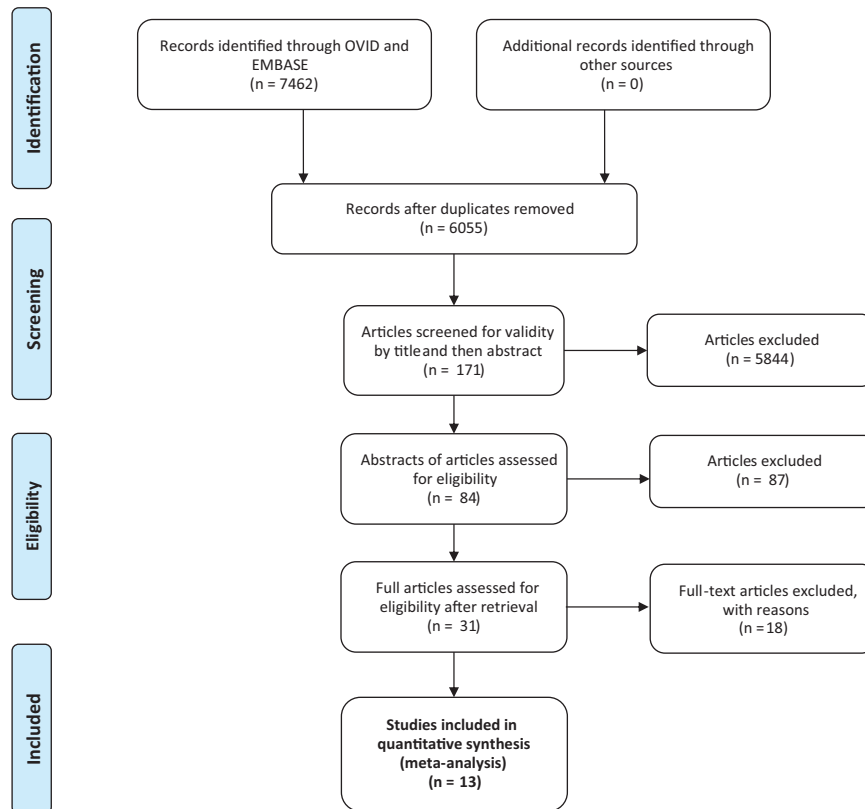


Figure 1. PRISMA flowchart.

desensitization starts with pretreatment with a leukotriene-modifying drug such as montelukast to decrease risk of lower airway reactions during aspirin exposure.^{5,6} This is followed by incremental exposure of aspirin in 30-, 60-, or 90-minute intervals, determined by the institution. Early studies utilized aspirin doses ranging from 300 to 2600 mg/d; however, current studies show symptomatic reactions between 40 and 160 mg.⁸ Generally, patients' symptoms are controlled medically before continuing escalation of dose until reaching the target dose of aspirin. Afterward, patients with AERD will remain on a daily aspirin dose that may be adjusted per clinical improvement.

The objective of this study is to describe the treatment outcomes of aspirin desensitization in patients with AERD through a systematic review and meta-analysis. To our knowledge, no previous meta-analysis was performed to evaluate the effects of aspirin desensitization on sinopulmonary outcomes.

Materials and Methods

Data Sources and Searches

A systematic review of the literature via OVID and Embase was conducted after the search protocol was implemented. A list of keywords and MeSH terms related to asthma, Samter's triad, AERD, aspirin, and NSAIDs was used as seen in Appendix 1 (available online). Two reviewers independently searched the literature, and articles were gathered in February 2019. Studies were included if they contained

publishable data. There were no restrictions on the language of the articles, and articles were translated to be used in the analysis.

Study Eligibility

Studies were evaluated that concerned participants who underwent aspirin desensitization and eventual daily therapy with aspirin. Inclusion criteria included studies that had patients with documented AERD, utilized a detailed desensitization protocol, and were randomized controlled trials (RCTs) or case series with comparable data. Exclusion criteria included articles that did not evaluate sinopulmonary outcomes, did not include a detailed desensitization protocol and aspirin regimen, or had irretrievable or repeated published data.

Data Extraction and Assessment

The PRISMA flowchart of the study is presented in **Figure 1**. A total of 7462 articles were initially reviewed for eligibility. Two authors independently screened the titles and the abstracts. Finally, studies with measurable or comparable outcomes of interest were deemed eligible for this study. Any disputes were met with discussion and, if need be, resolved by a third reviewer (M.R.C.). Reviewers used Mendeley software to remove duplicates and organize the articles in the search. The following information was extracted for our study: (1) study characteristics (authors, year of publication, country of origin, study design, sample

Table 1. Characteristics of the Studies Included in Our Analyses.

Study	Type of study	Blinding method	Quality (grade)	Country
Juergens (1995) ¹⁹	Cohort	—	3	USA
Mortazavi (2017) ¹⁴	RCT	DBPC	2	Iran
Lee (2010) ¹⁵	RCT	SB	2	USA
Esmailzadeh (2015) ¹⁶	RCT	DBPC	2	Iran
Makowska (2016) ²⁰	Cohort	—	3	Poland
Naeije (1984) ²¹	Cohort	—	4	Belgium
Świerczyńska-Krępa (2014) ²²	Cohort	—	3	Poland
Fruth (2013) ¹⁷	RCT	DBPC	2	Germany
Cho (2014) ²³	Cohort	—	3	USA
Jerschow (2017) ²⁴	Cohort	—	3	USA
McMains (2006) ¹⁸	RCT	Not specified	2	USA
Adappa (2018) ²⁵	Cohort	—	3	USA
Tyrak (2016) ²⁶	Cohort	—	3	Poland

Abbreviations: DBPC, double-blind placebo controlled; RCT, randomized controlled trial; SB, single blinded.

size), (2) patient demographics (age, sex), (3) inclusion and exclusion criteria, and (4) treatment dosage (maintenance aspirin, <650 mg; higher dose of aspirin, >650 mg). Using the Cochrane Collaboration's tool for assessing risk of bias, 2 authors (A.E.W. and M.R.C.) independently reviewed the articles.⁹

Outcomes Measured

Sinonasal Outcomes. Comparable studies of the meta-analysis were organized in the following categories:

- Endoscopic polyp grading
- Change in radiologic severity of chronic rhinosinusitis (Lund-McKay score)
- Sinus quality-of-life scores, including the Sino-Nasal Outcome Test (SNOT-22 or SNOT-20), Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), and the Rhinosinusitis Disability Index (RSDI), or sense-of-smell test scores (Sniffin Sticks; Burghardt)

Pulmonary Outcomes. Pulmonary outcomes included forced expiratory volume in 1 second (FEV-1), asthma control test, and asthma medication (oral or inhaled steroid) measured in amount used per day.

For clinical trials or cohort studies with 2 independent groups, the mean and standard deviation (SD) were used in the analyses for the differences in study outcomes between the treatment and control groups. For cohort studies without a control group, the mean and SD were used in the analyses for the difference in study outcomes before and after treatment on the same patients. Most studies did not report variation in the difference before and after treatment, and pooled SDs were estimated with the reported treatment and control groups' SDs and sample sizes. For studies that reported quartiles instead of SDs, we estimated SDs based on methods published by Wan et al in 2014.¹⁰

Study Quality Assessment

Studies were graded according to the guidelines published by the Center of Evidence Based Medicine¹¹:

Level 1: Good-quality RCT

Level 2: Low-quality RCT or good-quality cohort

Level 3: Case-control study, good-quality retrospective cohort

Level 4: Poor-quality cohort study or case series

Level 5: Expert opinion

Statistical Analysis

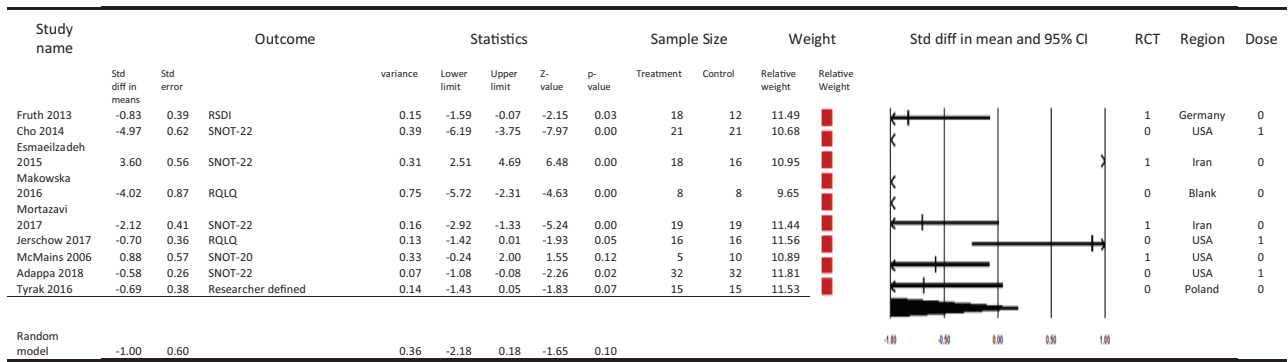
We computed the standardized mean difference (SMD) in each study for each outcome and then used a random effect model to estimate the overall difference. Weights and forest plots were reported for description. We also examined heterogeneity with Cochran's Q test and I^2 . If heterogeneity were detected, we conducted stratified analyses by covariates to ensure homogeneity within subgroups. We applied Egger's test¹² and Begg and Mazumdar's test¹³ to detect publication bias. All computation was performed by Comprehensive Meta-analysis (version 3; Biostat).

Results

Study Characteristics

Review of the OVID and Embase databases for unique studies revealed 6055 articles. A total of 13 articles were identified per the inclusion and exclusion criteria. General characteristics of the studies are listed in **Table 1**. The studies were published between 1984 and 2018. There were 5 RCTs¹⁴⁻¹⁸ and 8 cohorts.¹⁹⁻²⁶ From the 13 studies retrieved, 6 were performed in the United States, 3 in Poland, 2 in Iran, 1 in Belgium, and 1 in Germany. Ten studies had a scheduled follow-up period,^{14-17,20,22-26} while 3 studies had variable periods of follow-up.^{18,19,21}

Sinus Quality of Life Score



Significant heterogeneity (Cochran's Q : $p = 0.000$, $I^2 = 94.34$). Publication Bias: Egger's $p = 0.67$. Begg and Mazumdar $p = 0.25$

Figure 2. Forest plot with study weights for sinonasal quality-of-life outcome. Five studies utilized SNOT-20/SNOT-22 scoring, 2 RQLQ, 1 RSDI, and 1 researcher defined. Confidence intervals at the "0" line indicate no significant difference. RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; RSDI, Rhinosinusitis Disability Index; SNOT, Sino-Nasal Outcome Test.

Smell Score



Significant heterogeneity (Cochran's Q : $p = 0.000$, $I^2 = 94.130$). Publication Bias: too few studies.

Figure 3. Forest plot for the sense-of-smell outcome. The study weights and confidence intervals are included for both studies. Confidence intervals at the "0" line indicate no significant difference. RCT, randomized controlled trial.

Sinonasal Outcomes

The sinus quality-of-life scores were compared among 9 studies retrieved (**Figure 2**). Five studies used SNOT-20/SNOT-22 scores as outcome measures, 2 used RQLQ, and 1 used RSDI. The scores were mapped to the [0,1] interval for standardization of the scoring systems. There was no significant improvement in sinonasal quality of life with aspirin desensitization ($SMD = -1$, $P = .098$). Overall, there was heterogeneity in the studies that examined sinonasal quality-of-life scores. Stratifying the studies into paired and independent 2-sample t test still showed heterogeneity in the studies. No study performed an independent 2-sample t test with a high maintenance dose of aspirin.

Regarding smell scores, no significant improvement was seen in treatment groups. There was heterogeneity in the studies included (Cochran's Q : $P < .0001$, $I^2 = 94.13$; **Figure 3**).

Of the 13 studies that utilized endoscopic polyp grading, 2 were compared,^{17,23} and there was significant heterogeneity (Cochran's Q : $P < .0001$, $I^2 = 97.49$).

Regarding Lund-McKay scores, 4 studies included this outcome with no significant results with pooled analysis. There was no heterogeneity in the studies (**Figure 4**).

Pulmonary Outcomes

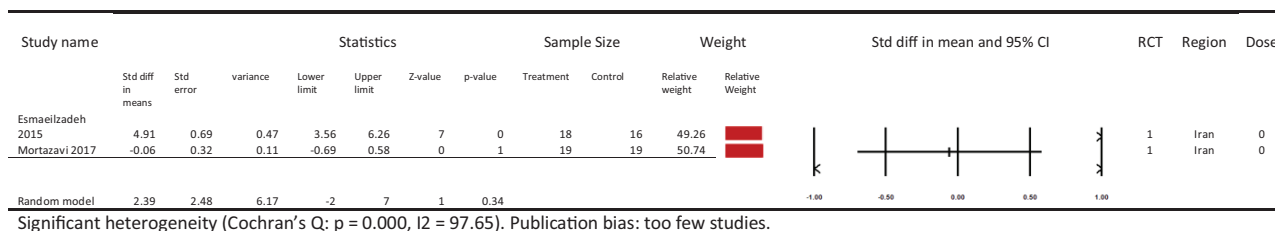
Pooled analyses of the 3 studies that included medication/steroid use showed a statistically significant reduction in the use of medications ($SMD = -0.792$, $P < .0001$; **Figure 5**). There was no significant heterogeneity in the studies (Cochran's Q : $P = .721$, $I^2 = 0.000$).

Regarding FEV-1, there was a statistically significant improvement ($SMD = 0.451$, $P = .031$) in the analyses of studies that included this outcome measure (**Figure 6**). Additionally, there was no significant heterogeneity (Cochran's Q : $P = .292$, $I^2 = 19.337$) in the studies.

Discussion

AERD significantly affects sinonasal and pulmonary quality of life. Treatment often consists of medical management of asthma and associated chronic rhinosinusitis. Patients often require sinus surgery with the goal of removing polyps and maintaining patent sinuses for topical delivery of steroid irrigations. Treatment that targets the phenotype of the disease, such as aspirin desensitization, should be explored as an option to stabilize the disease and avoid revision sinus surgery. Over the past 4 decades, there has been a growing

Lund Mckay (Independent)



Lund Mckay (Paired)

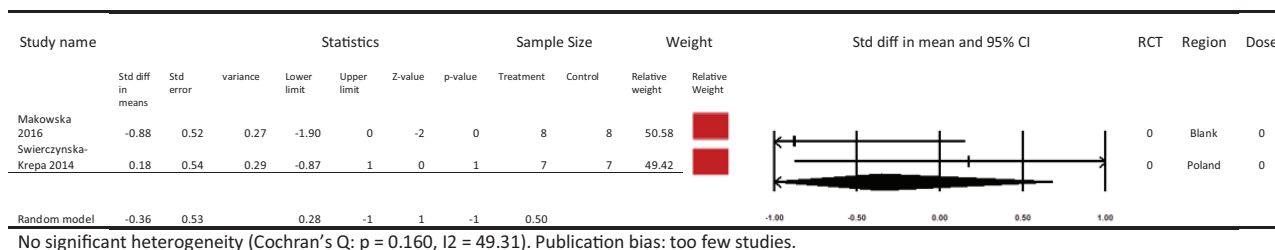


Figure 4. Forest plot for Lund-McKay outcome. The study weights and confidence intervals are included for all the studies and divided into independent and paired. Confidence intervals at the "0" line indicate no significant difference. RCT, randomized controlled trial.

Change in Medication/ Steroid Use

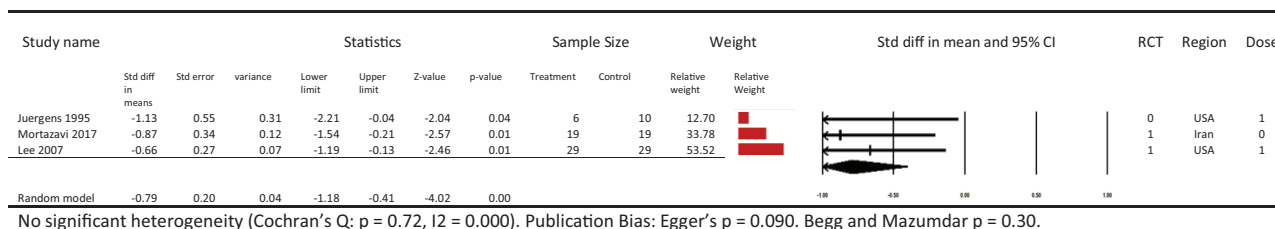


Figure 5. Forest plot for change in medication/steroid use. A total of 3 studies were included with their weights represented in the table and confidence intervals. Confidence intervals at the "0" line indicate no significant difference. RCT, randomized controlled trial.

FEV1

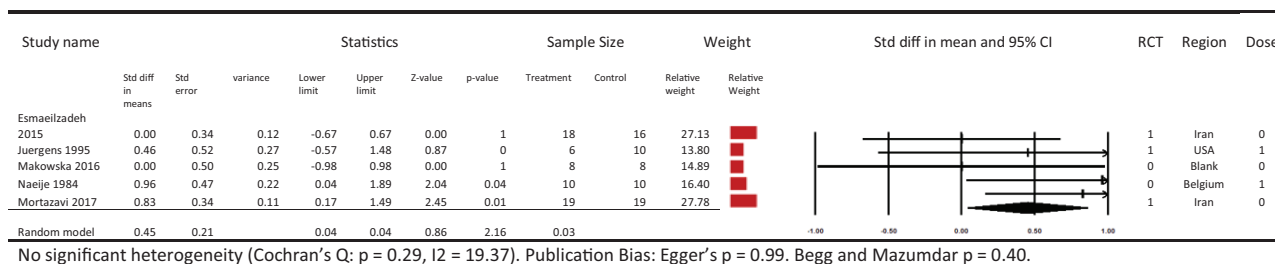


Figure 6. Forest plot for FEV1. A total of 5 studies were included. The study weights and confidence intervals are included for all the studies. Confidence intervals at the "0" line indicate no significant difference. FEV1, forced expiratory volume in 1 second; RCT, randomized controlled trial.

interest in aspirin desensitization treatments for patients with AERD. Despite reported benefits of aspirin desensitization,^{27,28} there is significant variation in the degree of improvements and in the outcomes measured. To date, no study has performed a meta-analysis examining the sinopulmonary outcomes of aspirin desensitization in patients with AERD.

Aspirin desensitization has evolved over the years with variable protocols involving the appropriate desensitization dosing schedule, maintenance dose, and treatment setting. Thus far, there has been no standardized protocol for aspirin desensitization. In our included studies, the maintenance dose was highly variable between 100 mg¹⁷ and 1300 mg daily.^{16,19,23,24} In addition, the duration of follow-up was

variable between 1 month¹⁵ and 36 months,¹⁷ with most studies examining 6-month outcomes. Despite earlier studies reporting a high discontinuation rate (up to 30%) of aspirin desensitization due to gastrointestinal irritation,^{29,30} aspirin desensitization appears to be safe. The dropout rate in our studies due to gastrointestinal side effects was low between 0% and 5.5%, with only 1 study reporting it as high as 33%.²² The gastrointestinal side effects do not seem to correlate with the maintenance dose of aspirin. The maintenance dose aspirin in the study with the highest rate (33%) of gastrointestinal side effects was 624 mg daily,²² which is lower than the reported rates of 0% to 5.5% in the studies that used a high maintenance dose of aspirin of 1300 mg.^{14–19,24} Additionally, most of the adverse events in the studies were related to gastrointestinal irritation or dyspepsia and rarely related to gastrointestinal bleeding.

When focusing on the outcomes of aspirin desensitization in patients with AERD, our analysis showed its efficacy to be strongest in improving pulmonary outcomes. This has not been shown previously, as the studies by Xu et al and Levy et al examined only sinonasal outcomes.^{31,32} Additionally, our recorded sinopulmonary outcomes were compiled as a meta-analysis and included recent RCTs and prospective cohorts that were not part of the studies by Xu et al and Levy et al. When all the studies that focused on FEV-1 as an outcome were combined, aspirin desensitization significantly improved FEV-1 values. Three of these 5 studies were RCTs,^{14,16,19} with the 2 largest ones^{14,16} from the same country (Iran) but with conflicting results in the control group. Esmailzadeh et al¹⁶ showed a significant improvement in FEV-1 in the control (placebo) and treatment (aspirin) groups. In both these large RCTs,^{14–16} it was unclear whether changes in FEV-1 reflected better control of asthma since there was no significant difference in the number of asthma exacerbations between the treatment and control groups. This could be related to the low number of visits in both groups, and more studies are needed to clarify this issue. The other pulmonary outcome that was used in studies was the change in medication and oral steroid use following aspirin desensitization. Our analysis of the 3 studies showed a significant decline in the use of asthma medications and oral steroids.

Regarding sinonasal outcomes, 9 studies included patient self-reported symptom questionnaires, such as SNOT-20/SNOT-22, RSDI, and RQLQ. Most of the studies examined the validated Sino-Nasal Outcome Test (SNOT-20 or SNOT-22). Four of these studies were RCTs. There was no statistically significant difference in sinonasal quality-of-life scores in patients who underwent aspirin desensitization. When our results were stratified into low- and high-maintenance dose aspirin regimen, patients who received a high maintenance dose (>650 mg) of aspirin had a significant improvement in their SNOT-22 scores in 2 studies^{23,25} with 1 study showing nonsignificant results.²⁴ All other

studies, regardless of the outcome assessment tool, had no significant improvement in sinonasal quality-of-life scores following aspirin desensitization. The 4 RCTs^{14,16–18} that included low-dose aspirin failed to show any significant change in sinonasal quality-of-life scores. The lack of improvement in this particular outcome is largely related to the significant heterogeneity in these identified studies. The other sinonasal outcome test that we examined was olfaction, and pooled analysis did not show any significant change in smell scores with aspirin desensitization.

Despite the overall positive results and few adverse events, it is still hard to predict which patients will respond favorably and what the ideal maintenance dose is. Further studies should look into the efficacy of the standardization of the aspirin regimen and outline a customized treatment plan per patient. The difficulty in conducting such studies is related to assessing the true therapeutic effects, as most patients still need to take steroids, antileukotrienes, or beta agonist due to AERD. The reported sources of variability in the response of patients to aspirin desensitization include race and severity of the underlying disease process. Individual patient variations extend to race, with African American and Latino patients being more likely to have symptom worsening with aspirin or failure to complete the initial desensitization as compared with white non-Latino patients ($P = .02$).²⁴ This exemplifies the importance of finding a standardized desensitization regimen with appropriate dosing schedule.

Our study has several limitations. First, there was significant heterogeneity in the studies, particularly the ones that focused on sinonasal outcomes. Second, patient selection could be an issue given the variability of the disease burden, with some patients being allowed to continue to use their rescue inhalers, leukotrienes, and steroids to avoid being dropped from the study. Finally, it is hard to predict which patients will encounter adverse events, as some patients dropped out of the studies.

Despite the clear benefit of this treatment, further studies are needed to determine which patients will truly benefit, whether or not this treatment is superior to other treatment modalities in patients with AERD, and at what point this treatment is initiated when surgery is contemplated, as patients who need extensive surgery will need to be off the aspirin to avoid bleeding.

Conclusion

There is an overall paucity of well-designed RCTs examining the sinopulmonary outcomes of aspirin desensitization in patients with AERD. However, given the current literature and few adverse effects of this treatment modality, there appears to be a clear benefit of this treatment in reducing FEV-1 and medication use for asthma in improving pulmonary outcomes. A standardized protocol tailored to individual patients needs to be established, as this treatment should be included in the management algorithm of patients with AERD.

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Author Contributions

Mohamad R. Chaaban, design of the work, drafting the work or revising it critically for important intellectual content, and final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **David Moffatt**, acquisition of the data, draft, and agreement and accountability to all work; **Alex E. Wright**, acquisition of data, draft, and agreement to final version and accountability to all aspects of the work; **James A. Cowthran**, analysis, draft, agreement to final version and accountable to all aspects of the work; **En Shuo Hsu**, analysis, draft methods, agreement of accountability to all work; **Yong-Fang Kuo**, analysis, design, draft, agreement and accountability of all work.

Disclosures

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Supplemental Material

Additional supporting information is available in the online version of the article.

References

- Walgama ES, Hwang PH. Aspirin-exacerbated respiratory disease. *Otolaryngol Clin North Am*. 2017;50(1):83-94.
- White AA, Stevenson DD. Aspirin-exacerbated respiratory disease. *N Engl J Med*. 2018;379(23):2281-2282.
- Stevenson DD, Simon RA, Mathison DA. Aspirin-sensitive asthma: tolerance to aspirin after positive oral aspirin challenges. *J Allergy Clin Immunol*. 1980;66(1):82-88.
- Waldram JD, Simon RA. Performing aspirin desensitization in aspirin-exacerbated respiratory disease. *Immunol Allergy Clin North Am*. 2016;36(4):693-703.
- Modena B, White AA, Woessner KM. Aspirin and nonsteroidal antiinflammatory drugs hypersensitivity and management. *Immunol Allergy Clin North Am*. 2017;37(4):727-749.
- White AA, Stevenson DD. Aspirin desensitization: faster protocols for busy patients. *J Allergy Clin Immunol Pract*. 2019;7(4):1181-1183.
- 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(6):1253-1255.
- Cortellini G, Caruso C, Romano A. Aspirin challenge and desensitization: how, when and why. *Curr Opin Allergy Clin Immunol*. 2017;17(4):247-254.
- Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
- Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
- Higgins J, Altman D, Sterne J. Assessing risk of bias in included studies. In: Higgins J, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration; 2009.
- Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
- Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088-1101.
- Mortazavi N, Esmaeilzadeh H, Abbasinazari M, et al. Clinical and immunological efficacy of aspirin desensitization in nasal polyp patients with aspirin-exacerbated respiratory disease. *Iran J Pharm Res*. 2017;16(4):1639-1647.
- Lee RU, White AA, Ding D, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2010;105(2):130-135.
- Esmaeilzadeh H, Nabavi M, Aryan Z, et al. Aspirin desensitization for patients with aspirin-exacerbated respiratory disease: a randomized double-blind placebo-controlled trial. *Clin Immunol*. 2015;160(2):349-357.
- Fruth K, Pogorzelski B, Schmidtman I, et al. Low-dose aspirin desensitization in individuals with aspirin-exacerbated respiratory disease. *Allergy*. 2013;68(5):659-665.
- McMains KC, Kountakis SE. Medical and surgical considerations in patients with Samter's triad. *Am J Rhinol*. 2006;20(6):573-576.
- Juergens UR, Christiansen SC, Stevenson DD, et al. Inhibition of monocyte leukotriene B4 production after aspirin desensitization. *Allergy Clin Immunol*. 1995;96(2):148-156.
- Makowska JS, Olszewska-Zięber A, Bienkiewicz B, et al. Clinical benefits of aspirin desensitization in patients with non-steroidal anti-inflammatory drug exacerbated respiratory disease are not related to urinary eicosanoid release and are accompanied with decreased urine creatinine. *Allergy Asthma Proc*. 2016;37(3):216-224.
- Naeije N, Bracamonte M, Michel O, et al. Effects of chronic aspirin ingestion in aspirin-intolerant asthmatic patients. *Ann Allergy*. 1984;53(3):262-254.
- Świerczyńska-Krępa M, Sanak M, Bochenek G, et al. Aspirin desensitization in patients with aspirin-induced and aspirin-tolerant asthma: a double-blind study. *J Allergy Clin Immunol*. 2014;134(4):883-890.
- Cho KS, Soudry E, Psaltis AJ, et al. Long-term sinonasal outcomes of aspirin desensitization in aspirin exacerbated respiratory disease. *Otolaryngol Head Neck Surg*. 2014;151(4):575-581.
- Jerschow E, Edin ML, Pelletier T, et al. Plasma 15-hydroxyeicosatetraenoic acid predicts treatment outcomes in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2017;5(4):998-1007.
- Adappa ND, Ranasinghe VJ, Trope M, et al. Outcomes after complete endoscopic sinus surgery and aspirin desensitization

- in aspirin-exacerbated respiratory disease. *Int Forum Allergy Rhinol.* 2018;8(1):49-53.
26. Tyrak KE, Mejza F, Buczek M, et al. Clinical and biochemical factors for response to aspirin desensitization in aspirin-induced asthma patients—pilot study. *Przegl Lek.* 2016;73(12):781-785.
27. Rozsasi A, Polzehl D, Deutschle T, et al. Long-term treatment with aspirin desensitization: a prospective clinical trial comparing 100 and 300 mg aspirin daily. *Allergy.* 2008;63(9):1228-1234.
28. Hope AP, Woessner KA, Simon RA, et al. Rational approach to aspirin dosing during oral challenges and desensitization of patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol.* 2009;123(2):406-410.
29. Stevenson DD, Hankammer MA, Mathison DA, et al. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. *J Allergy Clin Immunol.* 1996;98:751-758.
30. Sweet JM, Stevenson DD, Simon RA, et al. Long-term effects of aspirin desensitization-treatment for aspirin-sensitive rhinosinusitis-asthma. *J Allergy Clin Immunol.* 1990;8:59-65.
31. Xu JJ, Sowerby L, Rotenberg BW. Aspirin desensitization for aspirin-exacerbated respiratory disease (Samter's triad): a systematic review of the literature. *Int Forum Allergy Rhinol.* 2013;3(11):915-920.
32. Levy JM, Rudmik L, Peters AT, et al. Contemporary management of chronic rhinosinusitis with nasal polyposis in aspirin exacerbated respiratory disease: an evidence-based review with recommendations. *Int Forum Allergy Rhinol.* 2016;6(12):1273-1283.