STANFORD
UNIVERSITY

Biologic Therapy is NOT Preferred Over Aspirin Desensitization for AERD Treatment

Carlos A. Salgado
Allergy and Immunology Fellow
Stanford University
12/8/21

Objectives

- Present aspirin (ASA) desensitization efficacy, safety and tolerability.

- Discuss ASA desensitization cost effectiveness as compared to biologics.

What we know

- ASA desensitization and maintenance therapy is effective in treating nasal sinus and asthma symptoms both subjectively and objectively.
- ASA desensitization is a safe procedure and it is well tolerated.
- ASA desensitization and maintenance is undeniably cost effective as compared to biologic therapy.

History

- First ASA desensitization described in a single patient in 1922 and then in the 1970s.

- In 1980, Stevenson et al. reported 2 patients with AERD who underwent ASA desensitization and reported positive clinical outcomes after staying on a daily ASA regimen.

- Multiple observational and double-blind placebo-controlled studies have followed since.

ASA desensitization efficacy

- Stevens et al.[1] presented 14 different case series with a total of 847 patients and 5 placebo controlled studies with a total of 203 patients undergoing ASA desensitization.

American Academy of Allergy Asthma & Immunology

The role of aspirin desensitization followed by oral aspirin therapy in managing patients with aspirin-exacerbated respiratory disease: A Work Group Report from the Rhinitis, Rhinosinusitis and Ocular Allergy Committee of the American Academy of Allergy, Asthma & Immunology

Check for updates

Whitney W. Stevens, MD, PhD,[a] Elina Jerschow, MD,[b] Alan P. Baptist, MD, MPH,[c] Larry Borish, MD,[d] John V. Bosso, MD,[e] Kathleen M. Buchheit, MD,[f] Katherine N. Cahill, MD,[g] Paloma Campo, MD,[h] Seong H. Cho, MD,[i] Anjeni Keswani, MD,[j] Joshua M. Levy, MD, MPH,[k] Anil Nanda, MD,[l,m] Tanya M. Laidlaw, MD,[f] and Andrew A. White, MD[n] *Chicago, Ill; Bronx, NY; Ann Arbor, Mich; Charlottesville, Va; Philadelphia, Pa; Boston, Mass; Nashville, Tenn; Málaga, Spain; Tampa, Fla; Washington, DC; Lewisville, Flower Mound, and Dallas, Tex; and San Diego, Calif*

ASA desensitization efficacy

- Berges-Gimeno, et al.[2] performed a longitudinal study of 172 patients with AERD undergoing ASA desensitization.

- By 6 months of aspirin treatment, significant reduction in sinus infections and numbers of short courses of prednisone treatment.

- Improvements in sense of smell and general assessment of nasal-sinus and asthma symptoms.

ASA desensitization efficacy

TABLE III. Analysis of treatment with corticosteroids before, at 6 months after, and greater than 1 year after starting aspirin desensitization therapy

	Baseline		Aspirin treatment at 6 mo			Aspirin treatment at >1 y		
	Mean	SEM	Mean	SEM	*P* value*	Mean	SEM	*P* value*
Nasal corticosteroids (μg/d)	271.4	10.3	252.2	10.5	.004	216.3	15.0	<.0001
Inhaled corticosteroids (μg/d)	867.3	52.1	829.9	49.2	.06	656.7	35.4	<.0001
Daily corticosteroids (mg/d)	10.8	1.8	8.1	1.6	.01	3.6	0.8	<.0001
Short courses of corticosteroids/y	2.7	0.7	0.8	0.9	<.0001	0.5	1.3	<.0001

Values were determined with the paired *t* test.

*Comparisons were made between baseline and 6 months and baseline and greater than 1 year.

Berges-Gimeno, et al.[2]

ASA desensitization efficacy

- Addapa et al.[3] demonstrated that AERD patients had significant reduction in SNOT-22 scores post surgery and scores were maintained post desensitization for the follow up period.

TABLE 1. Mixed-effects model estimates for SNOT-22 subscales*

	Pre-ESS	1 month post-ESS	1 month post-desensitization	30 months post-desensitization
SNOT-22 total	47.0 (39.0-55.1)	15.2 (7.3-23.1)***	20.7 (12.1-29.3)	22.6 (11.6-33.7)

*The *p* values at 1 month post-ESS compare estimates to pre-ESS (time = 0); *p* values at 1 and 30 months post-desensitization compare estimates to 1 month post-ESS to assess for a difference in the SNOT-22 trajectory over time after aspirin desensitization.
**$p < 0.010$.
***$p < 0.001$.
ESS = endoscopic sinus surgery; SNOT-22 = 22-item Sino-Nasal Outcomes Test.

ASA desensitization efficacy

- Similar results reported by Cho et al.[4] from a case series of 28 patients post ESS and ASA desensitization.

Table 1. Changes in Sinonasal Outcomes Test-22 (SNOT-22) during Aspirin Desensitization following Endoscopic Sinus Surgery (n = 21).[a]

Time Point	Nasal Blockage Subscore	Sense of Smell Subscore	Total SNOT-22
Preoperative	3.9 ± 1.2	4.1 ± 1.3	53.4 ± 12.4
POD 7	0.7 ± 0.6[b]	1.2 ± 0.9[c]	14.5 ± 4.5[d]
POD 28/AD day 0	0.3 ± 0.7[e]	0.8 ± 1.1[e]	11.6 ± 2.5[f]
Post-AD 1 month	0.5 ± 0.8	1.3 ± 0.9	11.0 ± 2.3
Post-AD 6 months	0.4 ± 0.5	0.9 ± 0.4	9.2 ± 2.1
Post-AD 12 months	0.5 ± 0.7	1.1 ± 0.7	8.9 ± 1.7
Post-AD 18 months	0.3 ± 0.5	1.3 ± 0.5	8.6 ± 1.8
Post-AD 24 months	0.4 ± 0.5	1.4 ± 0.5	8.7 ± 1.6
Post-AD 30 months[g]	0.4 ± 0.5	1.3 ± 0.5	8.9 ± 1.7

Abbreviations: AD, aspirin desensitization; POD, postoperative day; SD, standard deviation.
[a]Data are expressed as mean ± SD.
[b]$P = .009$.
[c]$P = .019$.
[d]$P = .042$.
[e]$P < .001$.
[f]$P = .046$.
[g]Data are based on a subcohort of 13 patients.

ASA desensitization efficacy

- Rozsasi et al.[5] reported that compared to 100 mg of maintenance ASA, 300 mg daily aspirin therapy improved subjective measures as well as decreased need for revision surgery.

Table 2. Clinical follow-up parameters (median changes, i.e. values after 1 year of aspirin therapy minus pretreatment values) in seven patients taking 100 mg aspirin daily and seven patients taking 300 mg aspirin daily (Study-part one)

Follow-up parameters	100 group	300 group
Rhinomanometry-ND	−134	182*
Rhinomanometry+ND	−92	312*
Smell score	1	−3*
Sinusitis score	0	1 n.s.
Asthma score	0	0 n.s.
Spirometry improved (no. of patients)	0	5*
Reduced asthma medication (no.)	0	3*
Need of revision sinus surgery (no.)	7	0*

100 group, taking 100 mg aspirin daily; 300 group, taking 300 mg aspirin daily; −ND, without nasal decongestion; +ND, after nasal decongestion; statistics, Fisher's exact test or Mann–Whitney test; *$P < 0.05$; n.s., not significant.

ASA desensitization efficacy

- Chu et al.[6] meta analysis compared 5 randomized control trials and 2 comparative cohort studies.

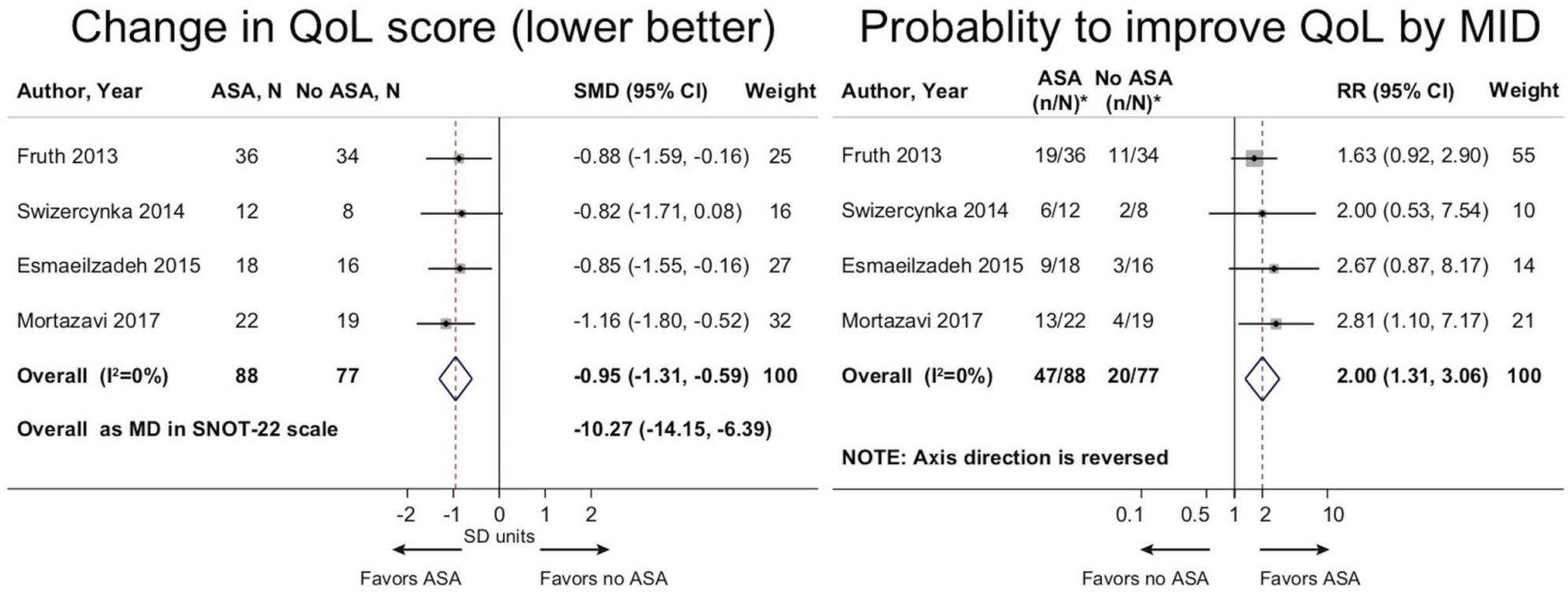

FIGURE 2. QoL outcomes in trials comparing aspirin desensitization vs placebo for AERD. *Estimated event frequency from probability to improve by MID. AERD = aspirin-exacerbated respiratory disease; ASA = acetylsalicylic acid (aspirin); MD = mean difference; MID = minimally important difference; QoL = quality of life; RR = risk ratio; SMD = standardized mean difference; SNOT-22 = 22-item Sino-Nasal Outcome Test (0 to 110, higher worse).

ASA desensitization efficacy

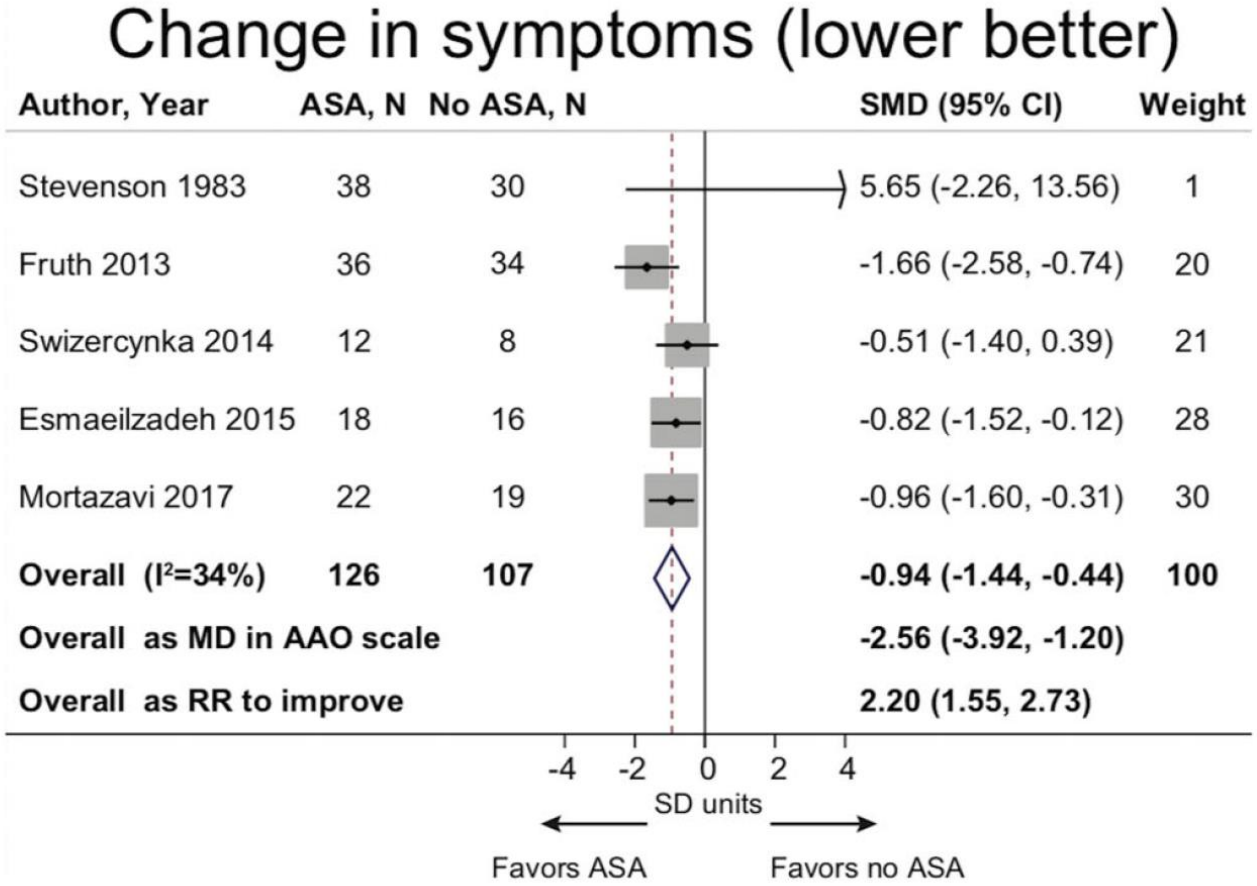

FIGURE 3. Respiratory symptom outcomes in trials comparing aspirin desensitization vs placebo for AERD. AAO scale = American Academy of Otolaryngology scale (0 to 20; higher worse); AERD = aspirin-exacerbated respiratory disease; ASA = acetylsalicylic acid (aspirin); MD = mean difference; p_{MC} = meta-regression *p* value calculated using 10,000 Monte Carlo random permutations; RR = risk ratio; SMD = standardized mean difference.

ASA desensitization efficacy

- Overall ASA desensitization and maintenance helps with:
  - Reduction of nasal symptoms.
  - Improvement of anosmia.
  - Decrease in requirement of intranasal steroids.
  - Decrease in recurrence rate of nasal polyps.
  - Delay in time to sinus revision surgery.
  - Improvement in asthma control.

ASA desensitization safety

- Protocols can be safely performed in an outpatient setting.
- Safety data does not support the need for a peripheral IV for a desensitization.
- No deaths due to physician-observed aspirin desensitization have ever been recorded.
- Leukotriene receptor antagonists should be used prior to a desensitization to reduce the severity of lower respiratory tract reactions.
- Desensitization should preferably be done 4-6 weeks after ESS to reduce the severity of reactions.

ASA desensitization safety

- Many studies have shown that patients rarely react to doses between 20 mg and 30 mg of ASA.

- Most common provocative doses are between 81 mg and 162 mg of ASA.

ASA desensitization protocols

TABLE V. Select aspirin desensitization protocols

		2-d protocols		1-d protocols		
Day	**Time**	**Oral aspirin[29]**	**Intranasal ketorolac and oral aspirin[96]**	**Oral aspirin[95]**	**Oral aspirin[84]**	**Oral aspirin[90]**
Day 1	8:00 am	20-40 mg	1.26 mg ketorolac (1 spray)	20.25 mg	41 mg	40 mg
	8:30 am		2.52 mg ketorolac (2 sprays)			
	9:00 am		5.04 mg ketorolac (4 sprays)			80 mg
	9:30 am		7.56 mg ketorolac (6 sprays)	40.5 mg	81 mg	
	10:00 am					160 mg
	10:30 am		60 mg aspirin			
	11:00 am	40-60 mg		81 mg	161 mg	325 mg
	11:30 am					
	12:00 pm		60 mg aspirin			Desensitization complete*
	12:30 pm			162.5 mg	325 mg	
	1:00 pm					
	1:30 pm		Instructions and discharge			
	2:00 pm	60-100 mg		325 mg	Desensitization complete*	
	2:30 pm					
	3:00 pm			Desensitization complete*		
	3:30 pm					
	4:00 pm					
	4:30 pm					
	5:00 pm	Instructions and discharge				
Day 2	8:00 am	100 mg	150 mg			
	11:00 am	160 mg	325 mg			
	2:00 pm	325 mg	Desensitization complete*			
	5:00 pm	Desensitization complete*				

*Actual time needed for the protocol to be completed may vary on the basis of severity of reaction and the time needed for recovery.

Stevens et al.[1]

ASA desensitization protocols

Patient safety and tolerability	
Time from provocative dose to reaction, mean (SD) in minutes	61 mins (22)
Reaction to repeat provoking dose, n (%)	0 (0)
Upper and lower respiratory reactions	
No reaction, n (%)	1 (2.3)
Bronchial only, n (%)	0 (0)
Naso-ocular only, n (%)	22 (50.0)
Bronchial and naso-ocular, n (%)	21 (47.7)
Extrapulmonary reactions	
Gastrointestinal, n (%)	10 (23.3)
Dermatologic, n (%)	8 (18.6)
Hypotension, n (%)	0 (0)
Significant lower respiratory symptoms	
No significant percent change in FEV1, n (%)	22 (51.2)
Significant percent change in FEV1, n (%)	21 (48.)
Change in FEV 1 among those with significant lower respiratory symptoms	
Minimum	−15%
25th percentile	−18%
Median	−25%
75th percentile	−31%
Maximum	−66%

DeGregorio, et al JACI IP [7]

ASA desensitization protocols

Number of nebulizer treatments (albuterol and/oripratropium) required, n (%)	
Zero nebulizer treatments	20 (45.5)
One nebulizer treatments	8 (18.6)
Two nebulizer treatments	8 (18.6)
Three or more nebulizer treatments	7 (16.3)

Feasibility of completion within 1-day	
Reached desensitization within one day, n (%)	41 (93.2)
Did not reach desensitization in one day, n (%)	3 (6.8)
Physician discontinuation for safety/tolerability	1 (2.3)
Patient choice	2 (4.6)
Average length of time per challenge/desensitization completed in 1 day (range)	9 hours and 29 mins (7 hrs 20 mins – 12 hrs)

DeGregorio, et al JACI IP 2019

Single day plus home escalation protocol

- Retrospective chart review of patients seen in the Stanford University AERD clinic.
- Novel desensitization protocol:
  - 3 doses of ASA, 90 minute intervals and 3 hour observation after final dose.
  - Starting dose 20.25 mg or 40.5 mg
  - Final clinic dose 81 mg or 162 mg.
  - Patients complete desensitization to goal dose at home with clear instructions.
  - Goal dose 650 mg ASA BID.

Single day plus home escalation protocol

- 27 patients underwent aspirin desensitization protocol.
- 25 patients (92.6%) completed the in-clinic portion
- Average clinic desensitization time under 6.5 hours.
- 22 patients (81.4%) completed home escalation to 650 mg BID.
- Average time to reach goal dose at home was 18.5 days.
- No reported lower respiratory reactions with home escalation.
- No patients required epinephrine, emergency room visits, or hospitalization.

Treatment for reactions during desensitization and maintenance

TABLE VI. Recommended pharmacologic treatment options for managing reactions induced during an aspirin desensitization in patients with AERD

Type of reaction	Pharmacologic options
Ocular	H_1R antagonists (ocular, oral)
Nasal	Decongestants (intranasal) H_1R antagonists (intranasal, oral) Corticosteroids (intranasal)
Laryngeal	Racemic epinephrine (inhaled) Epinephrine (intramuscular)
Respiratory	β_2-Agonists (inhaled) Anticholinergics (inhaled) Corticosteroids (oral)
Gastrointestinal	Antiemetics (oral) H_2R antagonists (oral) PPIs (oral) Epinephrine (intramuscular)
Skin	H_1R antagonists (oral)
Systemic	Epinephrine (intramuscular)

H_1R, Histamine 1 receptor.

Stevens et al.[1]

Contraindications to aspirin desensitization

- Planned sinus surgery
- Pregnancy
- Gastric ulcer or history of gastric bleeding (can be cleared by gastroenterologist)
- Bleeding disorders and coagulopathies
- Uncontrolled asthma
- Eosinophilic esophagitis

Aspirin maintenance duration

- 6 month ASA daily consumption trial recommended prior to assessing response.
- Minimum required dose for tolerance of cross reactive NSAIDs is 325 mg daily. Debate over which is the optimal dose for AERD symptom control.
- Interruption of therapy greater than 48 hours will result in loss of tolerance.

Emerging therapies

- Dupilumab (anti-IL-4Rα), omalizumab (anti IgE), mepolizumab (anti-IL-5) and benralizumab (anti-IL-5Rα) have been studied in patients with AERD.

ASA desensitization cost effectiveness

- List price of DUPIXENT is $3,203.39 USD per month ($38,447.04 per year).

- List price for aspirin is < $0.01 per pill (~$13 per year).

ASA desensitization cost effectiveness

- Yong et al.[8] performed a cost effective analysis comparing ASA desensitization and dupilumab for AERD.

- Primary outcomes were quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs).

- Four treatment strategies compared:
  - Patients receiving ASA desensitization after ESS
  - Patients receiving ASA desensitization after ESS with salvage dupilumab for those who failed ASA therapy
  - Patients receiving upfront dupilumab without ESS or ASA desensitization
  - Standard treatment, which consistent of appropriate medical management after ESS.

ASA desensitization cost effectiveness

TABLE 1 Cost-effectiveness rankings of strategies using 10-year time horizon

Strategy	Cost	QALYs	ICER
Standard treatment	$53,903.17	4.62	
ESS + ASA desensitization	$53,577.29	4.96	Dominant
ESS + ASA desensitization with salvage dupilumab	$121,011.44	5.46	$135,517.33
Upfront dupilumab	$185,919.07	5.70	$273,181.32

ASA = oral aspirin; ESS = endoscopic sinus surgery; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

Yong et al. IFAR 2021

ASA desensitization cost effectiveness

- ASA desensitization after ESS was cost-effective and dominated appropriate medical management.
- Salvage dupilumab was also considered cost effective under the willingness to pay threshold of $150,000.
- Upfront dupilumab without ESS or ASA desensitization was not cost effective.

Rebuttal

Objectives

- Bring attention to some of the downfalls of biologic therapy including short duration of symptom relief, small sample studies, limited therapy follow up, and concerning side effects.

Omalizumab

- Omalizumab improved severe asthma exacerbations and QOL after 6 months of therapy and allowed NSAID tolerance in 6 out of 7 patients in a case series. No mention on upper airway improvement or polyp recurrence. (Phillips-Angles, et al[9]).

- Double-blind, randomized, crossover, placebo-controlled, single-center study of 16 patient showed blunting of reaction to ASA in 62.5% of patients and improvement in ACT, ACQ-6, SNOT-22 though not clinically important differences. (Hayashi, et al[10])

Anti-IL-5/IL-5Rα monoclonal antibodies

- Retrospective chart review of AERD patients on anti-IL-5/IL-5Rα monoclonal antibodies who later switched to dupilumab (Bavaro, et al[11]).

- Patients had been on biologics for an average of 16 months before switching to dupilumab.

- Out of 47 patients, 27 (65.9%) transitioned to dupilumab for inadequately controlled upper and/or lower respiratory symptoms (remaining 14 continued on mepolizumab).

Anti-IL-5/IL-5Ra monoclonal antibodies

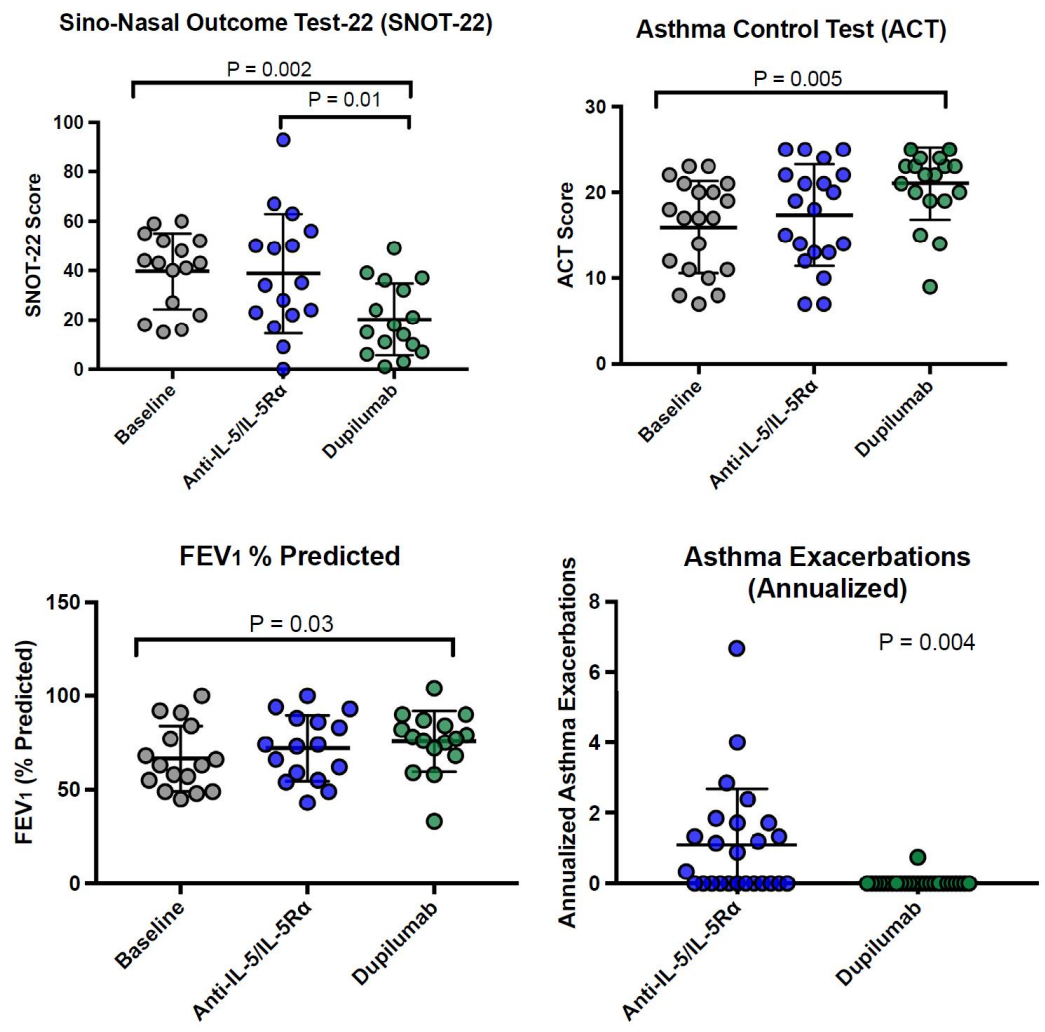

FIGURE 1. For subjects who switched to dupilumab, treatment with ≥60 days of dupilumab led to improved SNOT-22 score, ACT score, and FEV_1% predicted. Annualized asthma exacerbations decreased on dupilumab. Analysis with repeated-measures analysis of variance with *post hoc* Tukey's test or paired *t*-test. *FEV_1*, Forced expiratory volume in 1 second.

Bavaro, et al, JACI IP

Dupilumab

- Approved for asthma in 2018 and CRSwNP in 2019 so very limited existing data on long term effects or therapy failure.

- Studies looking at benefits only include the clinical trials and a few very small case series.

Dupilumab and eosinophilia

- Eosinophilia has been reported in dupilumab clinical trials for asthma and CRSwNP.
- In most cases eosinophils return to normal/lower levels after several weeks of therapy.
- Rare but reported cases of eosinophilic pneumonia, myositis and EGPA in patients with eosinophilia while on dupilumab.

Dupilumab and conjunctivitis

- Observed almost exclusively in the atopic dermatitis treatment group.
- Wide percentage of incidence ranging from 22% to 70% of patients on dupilumab.
- Recommended to have referral to ophthalmology as first-line therapy includes topical steroids and/or topical immunomodulators such as tacrolimus or cyclosporine.
- Often requires prolonged therapy.

Dupilumab and facial/neck erythema

- Not reported in the phase 3 trial for atopic dermatitis though happening in the real world.
- Jo, et al[12] reported 101 patients from 16 studies with dupilumab-associated facial or neck erythema.
- In the 57 patients with data on the course of the adverse events, improvement was observed in 29, clearance in 4, no response in 16, and worsening in 8.
- A total of 11 of 101 patients (11%) discontinued dupilumab owing to this adverse event.

Conclusions

- Aspirin desensitization is an effective (clinically and economically), safe, and well tolerated therapy for AERD.

- Studies looking at biologics for AERD are few, with limited number of patients and short follow up.

- Biologics are new and we have no long term data on clinical outcomes or side effects for these medications.

Conclusion

- “Targeted respiratory biologics represent a clinically significant advancement in our ability to improve treatment outcomes for recalcitrant type 2 inflammatory diseases such as AERD. However, these immunomodulatory medications are very costly; in addition, many of them do not yet have long-term safety or outcome data available and therefore are neither required by nor appropriate for all patients with AERD.”[13]

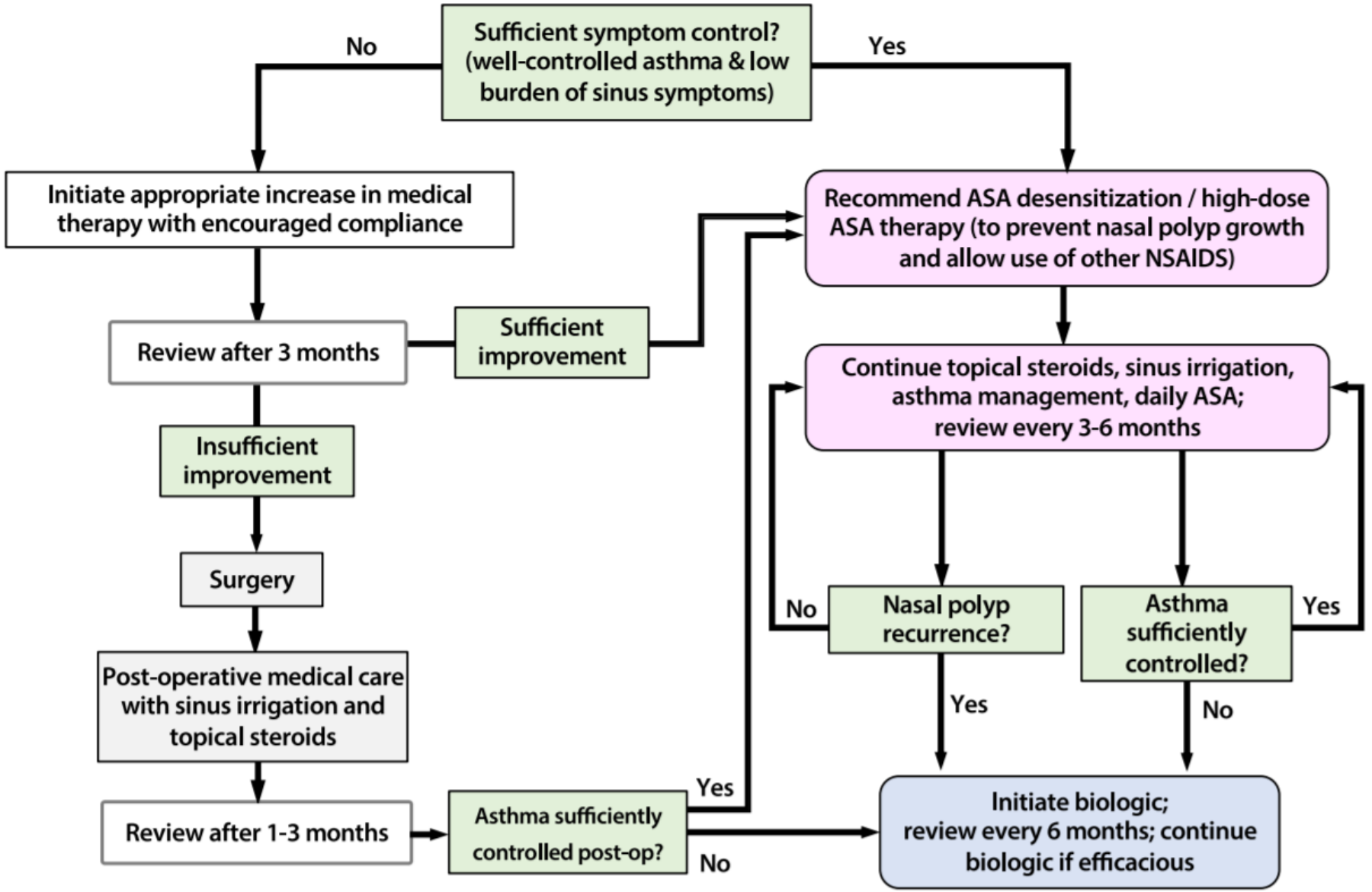

FIG 2. Proposed treatment algorithm for aspirin desensitization and targeted respiratory biologics for patients with AERD. *ASA*, Acetylsalicylic acid.

Buchheit et al, JACI 2021

References

1. Stevens WW, Jerschow E, Baptist AP, et al. The role of aspirin desensitization followed by oral aspirin therapy in managing patients with aspirin-exacerbated respiratory disease: A Work Group Report from the Rhinitis, Rhinosinusitis and Ocular Allergy Committee of the American Academy of Allergy, Asthma & Immunology. *Journal of Allergy and Clinical Immunology*. 2021;147(3):827-844. doi:10.1016/j.jaci.2020.10.043

2. Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *Journal of Allergy and Clinical Immunology*. 2003;111(1):180-186. doi:10.1067/mai.2003.7

3. Adappa ND, Ranasinghe VJ, Trope M, et al. Outcomes after complete endoscopic sinus surgery and aspirin desensitization in aspirin-exacerbated respiratory disease. *International Forum of Allergy & Rhinology*. 2018;8(1):49-53. doi:10.1002/alr.22036

4. 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. doi:10.1177/0194599814545750

5. 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. doi:10.1111/j.1398-9995.2008.01658.x

6. Chu DK, Lee DJ, Lee KM, Schünemann HJ, Szczeklik W, Lee JM. Benefits and harms of aspirin desensitization for aspirin-exacerbated respiratory disease: a systematic review and meta-analysis. *International Forum of Allergy & Rhinology*. 2019;9(12):1409-1419. doi:10.1002/alr.22428

7. DeGregorio GA, Singer J, Cahill KN, Laidlaw T. A one-day, 90-minute aspirin challenge and desensitization protocol in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2019;7(4):1174-1180. doi:10.1016/j.jaip.2018.10.032

8. Yong M, Wu YQ, Howlett J, Ballreich J, Walgama E, Thamboo A. Cost-effectiveness analysis comparing dupilumab and aspirin desensitization therapy for chronic rhinosinusitis with nasal polyposis in aspirin-exacerbated respiratory disease. *International Forum of Allergy & Rhinology*. n/a(n/a). doi:10.1002/alr.22865

9. Phillips-Angles E, Barranco P, Lluch-Bernal M, Dominguez-Ortega J, López-Carrasco V, Quirce S. Aspirin tolerance in patients with nonsteroidal anti-inflammatory drug–exacerbated respiratory disease following treatment with omalizumab. *The Journal of Allergy and Clinical Immunology: In Practice*. 2017;5(3):842-845. doi:10.1016/j.jaip.2016.12.013

10. Hayashi H, Fukutomi Y, Mitsui C, et al. Omalizumab for Aspirin Hypersensitivity and Leukotriene Overproduction in Aspirin-exacerbated Respiratory Disease. A Randomized Controlled Trial. *Am J Respir Crit Care Med*. 2020;201(12):1488-1498. doi:10.1164/rccm.201906-1215OC

11. Bavaro N, Gakpo D, Mittal A, Bensko JC, Laidlaw TM, Buchheit KM. Efficacy of dupilumab in patients with aspirin-exacerbated respiratory disease and previous inadequate response to anti-IL-5 or anti-IL-5Rα in a real-world setting. *The Journal of Allergy and Clinical Immunology: In Practice*. 2021;9(7):2910-2912.e1. doi:10.1016/j.jaip.2021.02.020

12. Jo CE, Finstad A, Georgakopoulos JR, Piguet V, Yeung J, Drucker AM. Facial and neck erythema associated with dupilumab treatment: A systematic review. *Journal of the American Academy of Dermatology*. 2021;84(5):1339-1347. doi:10.1016/j.jaad.2021.01.012

13. Buchheit KM, Laidlaw TM, Levy JM. Immunology-based recommendations for available and upcoming biologics in aspirin-exacerbated respiratory disease. *Journal of Allergy and Clinical Immunology*. 2021;148(2):348-350. doi:10.1016/j.jaci.2021.06.019