

Hypereosinophilia following aspirin desensitization for aspirin-exacerbated respiratory disease

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Clinical Implications

Hypereosinophilia can develop while receiving maintenance daily aspirin after undergoing aspirin desensitization for aspirin-exacerbated respiratory disease. Regular monitoring of eosinophil counts may be employed to detect this complication and provide early intervention.

Aspirin-exacerbated respiratory disease (AERD) is an inflammatory syndrome characterized by the triad of asthma, chronic rhinosinusitis with nasal polyposis, and sensitivity to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs).¹ Its pathogenesis is related to deranged arachidonic acid metabolism leading to elevated levels of cysteinyl leukotrienes (CysLTs) and prostaglandin D₂, both of which contribute to eosinophilia found in AERD.^{1,2} Aspirin desensitization followed by maintenance aspirin therapy has been shown to be beneficial at reducing symptoms in patients with AERD, although its mechanism for doing so remains unproven.^{1,3-5} Multiple studies have shown paradoxical elevations in CysLTs and circulating eosinophils during desensitization and maintenance therapy, despite those biomarkers typically being associated with the disease itself.^{2,6-8} Specifically, absolute eosinophil counts (AECs) have been shown to increase from a baseline between 0.31 and $0.70 \times 10^9/L$ to a postdesensitization level ranging from 0.88 to $1.10 \times 10^9/L$.^{2,6,8} Although mild eosinophilia after desensitization is typically asymptomatic and requires no treatment, the development of hypereosinophilia, reported once previously, could warrant therapy or aspirin dose adjustments.^{2,6,9} In this study, we sought to determine the frequency of eosinophilia and hypereosinophilia after aspirin desensitization at a large academic medical center.

A retrospective chart review of patients who underwent aspirin desensitization for AERD at Mayo Clinic was performed including the following key elements: demographics, predesensitization medication regimen and laboratory values, postdesensitization AECs, and treatment details of postdesensitization eosinophilia. The choice to desensitize, protocol used, and treatment of postdesensitization eosinophilia were determined by each individual provider. AEC monitoring after desensitization was not necessarily done by the allergist for the purpose of eosinophilia detection, and many patients had levels checked by a nonallergy provider as part of routine clinical care.

Between January 1, 2018, and August 12, 2021, 97 patients underwent aspirin desensitization, 23 of whom had pre- and postdesensitization AECs. A summary of demographics, clinical characteristics, laboratory values, and outcomes is shown in Table I. The mean AEC before desensitization was $0.53 \times 10^9/L$ (ref 0.03 - $0.48 \times 10^9/L$), and the mean urinary leukotriene E₄ level was 459.5 pg/mg creatinine (ref <104 pg/mg creatinine). After desensitization, the mean peak AEC increased by 0.35 from baseline to $0.88 \times 10^9/L$. The peak AEC occurred on average 262 days after desensitization and occurred while on a dose of

650 mg twice daily in 11 patients and 325 mg twice daily in 12 patients. Four patients developed hypereosinophilia (AEC $>1.50 \times 10^9/L$), the details of which are shown in Table II and Table E1 (available in this article's Online Repository at www.jaci-inpractice.org). Patient 1 developed an AEC of $2.80 \times 10^9/L$ 178 days after desensitization from a baseline of $0.66 \times 10^9/L$. She started mepolizumab 100 mg subcutaneously due to worsening asthma flares, and her eosinophilia resolved without changing her aspirin dose. Patient 2 developed an AEC of $2.23 \times 10^9/L$ 24 days after desensitization from a baseline of $0.90 \times 10^9/L$. He was asymptomatic, and his eosinophilia resolved without any treatment or aspirin dose adjustments. Patient 3 developed an AEC of $4.17 \times 10^9/L$ 49 days after desensitization from a baseline of $0.63 \times 10^9/L$. Her eosinophilia persisted despite a dose reduction to 325 mg bid, so she was treated with prednisone 20 mg for 5 days. Her eosinophilia improved but quickly rebounded to $1.81 \times 10^9/L$ after cessation of steroids. She developed chest pain with an elevated troponin and normal cardiac catheterization. Out of concern for end-organ eosinophilic involvement, her aspirin was stopped, and her AEC decreased to $0.57 \times 10^9/L$. She started dupilumab for worsening AERD, and her most recent AEC was $0.60 \times 10^9/L$. Patient 4 developed an AEC of $4.00 \times 10^9/L$ 49 days after desensitization from a baseline of $0.66 \times 10^9/L$. She received two 5-day courses of prednisone 40 mg with associated aspirin dose reductions, but no sustained improvement was seen until her aspirin dose was decreased to 325 mg daily. Her most recent AEC was $0.64 \times 10^9/L$. None of these patients used new medications or had their AERD regimen altered between aspirin desensitization and eosinophilia development.

Mild increases in AECs are frequently seen after aspirin desensitization in patients with AERD, although this often is asymptomatic and requires no treatment or aspirin dose reduction.^{2,6,8} Similarly, we demonstrated a mild increase in AEC from a baseline of $0.53 \times 10^9/L$ to $0.88 \times 10^9/L$ after desensitization. A unique aspect of our cohort is the number of patients who developed hypereosinophilia. Although previously reported only once, we found 4 patients who developed hypereosinophilia between 24 and 178 days after desensitization.⁹ Three of these patients received either eosinophilia-directed therapy or aspirin dose adjustments, whereas only 1 patient ceased aspirin therapy. There are currently no clear guidelines regarding duration of long-term aspirin therapy or need for lab monitoring after desensitization.¹ As such, our findings may suggest that regular monitoring of AECs after aspirin desensitization may need to be further explored. Although aspirin desensitization is the most cost-effective and well-studied treatment for AERD, the use of biologics provides an alternative therapy should symptomatic aspirin-induced hypereosinophilia occur. However, it should be noted that in many cases, asymptomatic eosinophilia likely can be observed without any intervention necessary. For example, AEC monitoring and medication adjustment are not necessarily routinely done while using dupilumab, even though asymptomatic AEC elevations can occur after its initiation. Although the same could be true of aspirin in AERD, if symptoms attributable to eosinophilia develop, treatment or aspirin dose adjustment could be revisited after a risk-benefit discussion with the patient.

TABLE I. Summary of demographics, laboratory values, and outcomes

Characteristic	Total (n = 23)	Female (n = 16)	Male (n = 7)
Age (y), mean (SD)	52.1 (14.7)	52.1 (15.3)	52.1 (13.5)
Race (%)			
White	21 (91.3)	16 (100)	5 (71.4)
Asian	1 (4.3)	0 (0)	1 (14.3)
Black	1 (4.3)	0 (0)	1 (14.3)
BMI, mean (SD)	28.7 (5.6)	28.6 (6.1)	29.0 (4.1)
Tobacco use (%)			
Never	13 (56.5)	9 (56.3)	4 (57.1)
Current	1 (4.3)	1 (6.3)	0 (0)
Former	9 (39.1)	6 (37.5)	3 (42.9)
Other atopic disease (%)	2 (8.7)	1 (6.3)	1 (14.3)
Baseline IgE*, mean (SD)	152.7 (208.6)	82.7 (57.1)	257.8 (292.4)
Baseline urine LTE ₄ *, mean (SD)	459.3 (613.9)	549.2 (713.4)	266.6 (199.1)
Baseline FEV ₁ % predicted, mean (SD)	92.3 (9.2)	92.9 (9.7)	90.7 (7.7)
Baseline eNO (ppb), mean (SD)	82.2 (95.8)	138.3 (109.8)	26.3 (2.1)
ICS potency (%)			
Low	4 (17.4)	2 (12.5)	2 (28.6)
Moderate	8 (34.8)	7 (43.8)	1 (14.3)
High	11 (47.8)	7 (43.8)	4 (57.1)
Montelukast (%)	23 (100)	16 (100)	7 (100)
Chronic systemic steroids (%)	0 (0)	0 (0)	0 (0)
Sinus surgery within 6 mo of desensitization (%)	18 (78.3)	14 (87.5)	4 (57.1)
Baseline AEC*, mean (SD)	0.53 (0.25)	0.55 (0.26)	0.47 (0.22)
Desensitization protocol			
Oral aspirin	5 (21.7)	3 (18.8)	2 (28.6)
Nasal ketorolac	18 (78.3)	13 (81.3)	5 (71.4)
Peak AEC* after desensitization, mean (SD)	0.88 (1.11)	1.07 (1.30)	0.63 (0.67)
Days between desensitization and peak AEC*, mean (SD)	255 (236)	313 (253)	125 (106)
Culprit aspirin dose (%)			
650 mg bid	11 (47.8)	8 (50)	3 (42.9)
325 mg bid	12 (52.2)	8 (50)	4 (57.1)
Aspirin stopped due to eosinophilia (%)	1 (4.3)	1 (6.3)	0 (0)
Treatment for eosinophilia (%)	3 (13.0)	3 (18.8)	0 (0)

AEC, absolute eosinophil count; BMI, body mass index; eNO, exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LTE₄, leukotriene E₄; ppb, parts per billion; SD, standard deviation.

*Reference ranges: IgE: <214 kU/L, LTE₄: <104 pg/mg creatinine; AEC: 0.03-0.48 × 10⁹/L.

Weaknesses of this study include the inability to definitively show that aspirin was the culprit for eosinophilia. Alternative explanations include the presence of another nonaspirin responsive disease process such as eosinophilic granulomatosis with polyangiitis or rebound eosinophilia following steroid tapering after aspirin desensitization. However, none of the patients met criteria for eosinophilic granulomatosis with polyangiitis, and none of them had alterations to their medication regimen between desensitization and eosinophilia discovery. In addition, no studies were performed to demonstrate eosinophilic organ infiltration, which is relevant for patient 3 in whom aspirin-induced eosinophilic myocarditis was being considered. Cardiac magnetic resonance imaging or an endomyocardial biopsy would have strengthened this hypothesis, but without these it cannot be determined whether her eosinophilia was the cause of her chest pain and troponinemia. In addition, as this study was conducted at a large academic institution, referral bias may limit generalizability of our findings to the general population. As such, conclusions to change current clinical practice guidelines cannot be made. Future prospective studies are

needed for patients with AERD undergoing aspirin desensitization to address the utility of systematic AEC monitoring in this population.

In summary, hypereosinophilia occurred in 4 of 23 (17%) patients who underwent aspirin desensitization for AERD in our cohort. Regular AEC monitoring after desensitization may be indicated to detect this complication.

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TABLE II. Characteristics of patients with hypereosinophilia after aspirin desensitization *

Patient	Age/sex	BMI	Race	Tobacco use	Other atopic disease	ICS potency	Baseline urine LTE ₄ †	Baseline eNO (ppb)	Baseline AEC‡	Highest AEC after desensitization‡	Days since desensitization	Culprit aspirin dose	Treatment	Outcome
1	55F	29.3	White	No	No	High	578	NA	0.66	1.66	295	325 mg bid	Mepolizumab‡	Resolved without aspirin dose change
2	49M	26.3	White	No	No	Moderate	494	NA	0.90	2.23	24	650 mg bid	None	Resolved without aspirin dose change
3	78F	21.9	White	No	No	High	615	283	0.63	4.17	49	650 mg bid	Prednisone§	Recurrence after prednisone burst, aspirin stopped
4	54F	31.4	White	No	No	Moderate	2959	115	1.08	4.00	119	650 mg bid	Prednisone	Improved after aspirin dose reduction to 325 mg daily

AEC, absolute eosinophil count; *bid*, twice daily; BMI, body mass index; *eNO*, exhaled nitric oxide; *ICS*, inhaled corticosteroid; *LTE₄*, leukotriene E₄; *ppb*, parts per billion.

*Each patient underwent a 2-day protocol using nasal ketorolac.

†Reference ranges: *LTE₄*: <104 pg/mg creatinine; AEC: 0.03-0.48 × 10⁹/L.

‡100 mg subcutaneous every 28 days, started due to worsening asthma flares.

§20 mg daily for 5 days.

||40 mg daily for 5 days.

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TABLE E1. Eosinophil trends in patients with postaspirin desensitization hypereosinophilia

Patient 1			Patient 2		
Date	AEC*	Timeline and notes	Date	AEC*	Timeline and notes
April 26, 2018	0.66	Desensitization August 8, 2018	December 17, 2018	0.9	
February 2, 2019	2.80		February 20, 2019	0.3	Desensitization 2/11/19
May 30, 2019	1.66	Nucala started due to worsening asthma	March 7, 2019	2.23	
August 19, 2019	0.67		June 18, 2019	0.29	
July 8, 2020	0.05		June 8, 2020	0.31	
May 28, 2021	0.12		September 30, 2020	0.27	
			June 27, 2021	0.28	
Patient 3			Patient 4		
Date	AEC*	Timeline and notes	Date	AEC*	Timeline and notes
June 10, 2019	1.07		May 4, 2018	0.6	
September 4, 2019	0.58		August 20, 2021	1.08	Desensitization 8/12/21
June 11, 2020	0.63	Desensitization October 14, 2020	September 23, 2021	3.80	Aspirin decreased to 325 mg bid
December 2, 2020	4.17	Aspirin decreased to 325 mg bid	September 30, 2021	3.20	40 mg prednisone ×5 d
December 7, 2020	3.15	Aspirin decreased to 325 mg daily, 20 mg prednisone ×5 d	December 9, 2021	4.00	Aspirin decreased to 325 mg daily
December 11, 2020	0.06		December 21, 2021	0.64	
December 17, 2020	1.81	Develops chest pain, troponinemia, normal cardiac catheterization, aspirin stopped, 20 mg prednisone ×5 d			
December 30, 2020	0.57	Dupilumab started due to worsening AERD			
June 14, 2021	0.80				
November 8, 2021	0.60				

AEC, absolute eosinophil count; AERD, aspirin-exacerbated respiratory disease.

*Reference range: $0.03\text{--}0.48 \times 10^9/\text{L}$.