

Aspirin-exacerbated respiratory disease: A syndrome of mast cell-mediated PgD2
overproduction

Larry Borish, MD

Professor of Medicine and Microbiology

University of Virginia Health Systems

Charlottesville, VA 22908-1355

Address for correspondence: Asthma and Allergic Disease Center, Box 801355, University
of Virginia Health System, Charlottesville, VA, 22908-1355; Fax #: (434) 924-5779, Phone
(434) 924-5917, email: lb4m@virginia.edu

Hypersensitivity reactions to aspirin were first described almost immediately after its introduction and by 1922 Widal had described the constellation of asthma and nasal polyps (NP) with aspirin sensitivity and also reported on the beneficial effects of aspirin desensitization. Currently, the preferred term for this syndrome is aspirin-exacerbated respiratory disease (AERD), recognizing that not all subjects have asthma. AERD patients often prove clinically challenging. Sinus surgery and polypectomy are often fruitless as the sinonasal disease rapidly recurs. Similarly, when present, the asthma component can produce a severe phenotype that is refractory to treatment and often associated with progressive irreversible obstruction.

While a clinical challenge, AERD does offer physicians two forms of therapy that are specific to this disorder: aspirin desensitization and leukotriene (LT) modifiers. A distinguishing feature of AERD is high constitutive production of cysteinyl leukotrienes (CysLTs) and a further surge during reactions to aspirin and other non-selective cyclooxygenase (COX) inhibitors (1). Reflecting the importance of CysLTs, LT modifiers and, in particular, leukotriene synthesis (5-lipoxygenase (5-LO)) inhibitors, reduce polyp size, restore sense of smell, and improve both sinus and asthma symptoms while reducing LTE₄ concentrations (2). These data appear to argue that CysLTs are primary mediators of AERD. Similarly, aspirin desensitization followed by continuous high dose administration of aspirin will suppress NP growth, improve sinus symptom scores, restore sense of smell, decrease frequency of secondary acute sinus infections, improve asthma control, and reduce the need for oral corticosteroids (3).

It was assumed that aspirin desensitization would work by recapitulating the pathways mediated by 5-LO inhibition, namely reduction in CysLT production. However, here, Cahill *et al.* investigated the effects of aspirin therapy on biomarkers of AERD (4). Surprisingly, this study demonstrated the paradox that high dose aspirin administration after desensitization increases numerous markers of allergic (type 2) inflammation and specifically actually further *increased* CysLT production (5). Thus, the two medical treatments we have for AERD have exactly opposite effects on what has been thought to be this central pathogenic mediator.

Finding an explanation for the increase in type 2 inflammation is more straightforward. In AERD, PgE2 primarily mediates anti-inflammatory effects and, specifically, it constrains the activation of eosinophils, basophils, mast cells, and other immune cells (6). The severe hypersensitivity reactions that occur in AERD in response to aspirin reflect the loss of this PgE2 inhibitory pathway as can be demonstrated by the ability of PgE2 homologs to block reactions (7). In the current study, the authors further support this concept by demonstrating that high dose aspirin lowers PgE2 concentrations and thereby enhances several aspects of allergic inflammation including enhanced mast cell activation with higher levels of tryptase and the CysLTs.

But how is it possible to reconcile this *increased* production of CysLTs with the clinical benefits observed? In addition to CysLT over-production, AERD is also characterized by

exquisite sensitivity to CysLTs, with CysLT challenges driving enhanced bronchospasm, eosinophil recruitment, and worsening of bronchial hyperreactivity (8). These effects are particularly profound with LTE4 challenges, likely reflecting LTE4 acting through the recently described LTE4 receptor (LTE4R)(9). One explanation for a clinical benefit of aspirin in the face of increased CysLT production would be if aspirin down-regulated CysLT receptors or signaling. Reduced CysLT receptor 1 expression does occur (10), although this is less likely to explain any therapeutic benefit given the usual disappointing results with LT receptor antagonists. Nor would this explain the specific decreases in sensitivity to LTE4 challenges (8), arguing perhaps for decreased expression of LTE4R. Reduced LTE4R transcript expression was not reported in the studies performed on peripheral blood in this study. But modulation of LTE4R expression has not been studied in NP or lung samples, studies clearly needing to be performed. A mechanism for reduced LT receptor expression could be mediated through the reported influences of aspirin on immune and signaling pathways (e.g., stat6, cytokine production)(11).

There is, however, another more intriguing mechanism by which aspirin could benefit AERD patients in the face of higher CysLT production. Specifically, perhaps all aspirin is accomplishing is exactly what would be predicted from its mode of action, that is, inhibition of cyclooxygenase. Consistent with COX inhibition, the current study also demonstrates lower thromboxane (Tx) and PgD2 production. Both Tx and PgD2 act through the Tx receptor (TP) to cause bronchospasm (12). But it is particularly intriguing to consider whether blockade of PgD2 acting through its type 2 receptor (DP2 or CRTH2) could be the primary basis for the clinical benefits observed with aspirin. CRTH2 is expressed on Th2

effector lymphocytes, innate lymphoid type 2 cells, basophils, and eosinophils and drives recruitment and activation of these cells (13). The increases in circulating CRTH2⁺ eosinophils and basophils in the circulation that was observed in the current study would be consistent with the “stranding” of these and likely other CRTH2⁺ cells in the circulation and result in their failure to ingress into respiratory tissue and impact inflammation.

It is then reasonable to speculate that both aspirin and 5-LO inhibitors benefit AERD through the same final common pathway, namely the blockade of PgD2 production. The LTE4 receptor is highly expressed on epithelial cells and mast cells. Engagement of these receptors on epithelial cells (14), in part through their secretion of IL-25, IL-33, and TSLP, can indirectly drive mast cell activation and PgD2 production. But CysLTs including especially LTE4, also act directly on mast cells to cause PgD2 production (15). Thus, an intriguing solution to the paradox of 5-LO inhibitors producing *decreased* CysLT expression and aspirin administration's *increased* CysLT expression both being beneficial in AERD would be that both agents ultimately act to decrease PgD2.

In summary, this study points to the central role of the mast cell in the pathogenesis of AERD with mast cell-derived PgD2 potentially being a central pathogenic mediator. And, any mechanism that blocks PgD2 pathways, including CysLT synthesis inhibitors, cyclooxygenase inhibitors, or perhaps in the future, CRTH2 antagonists, can form the basis for clinical improvement.

Bibliography

1. Mastalerz L, Sanak M, Gawlewicz-Mroccka A, Gielicz A, Cmiel A, Szczeklik A. Prostaglandin E2 systemic production in patients with asthma with and without aspirin hypersensitivity. *Thorax* 2008; 63: 27-34.
2. Dahlen B, Nizankowska E, Szczeklik A, Zetterstrom O, Bochenek G, Kumlin M, Mastalerz L, Pinis G, Swanson LJ, Boodhoo TI, Wright S, Dube LM, Dahlen SE. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 1998; 157: 1187-1194.
3. Woessner KM. Update on Aspirin-Exacerbated Respiratory Disease. *Current allergy and asthma reports* 2017; 17: 2.
4. Cahill KN, Cui J, Kothari P, Murphy K, Raby BA, Singer J, Israel E, Boyce JA, Laidlaw TM. Unique effects of aspirin therapy on biomarkers in aspirin-exacerbated respiratory disease: A Prospective Trial. *Am J Respir Crit Care Med* [online ahead of print] 12 April 2019; <https://www.atsjournals.org/doi/abs/10.1164/rccm.201809-17550C>.
5. Bobolea I, Del Pozo V, Sanz V, Cabanas R, Fiandor A, Alfonso-Carrillo C, Salcedo MA, Heredia Revuelto R, Quirce S. Aspirin desensitization in aspirin-exacerbated respiratory disease: New insights into the molecular mechanisms. *Respir Med* 2018; 143: 39-41.
6. Laidlaw TM, Boyce JA. Aspirin-Exacerbated Respiratory Disease--New Prime Suspects. *N Engl J Med* 2016; 374: 484-488.
7. Sestini P, Armetti L, Gambaro G, Pieroni MG, Refini RM, Sala A, Vaghi A, Folco GC, Bianco S, Robuschi M. Inhaled PGE2 prevents aspirin-induced bronchoconstriction and

- urinary LTE₄ excretion in aspirin-sensitive asthma. *American J Respiratory Critical Care Medicine* 1996; 153: 572-575.
8. Arm JP, O'Hickey SP, Spur BW, Lee TH. Airway responsiveness to histamine and leukotriene E₄ in subjects with aspirin-induced asthma. *Am Rev Respir Dis* 1989; 140: 148-153.
9. Maekawa A, Kanaoka Y, Xing W, Austen KF. Functional recognition of a distinct receptor preferential for leukotriene E₄ in mice lacking the cysteinyl leukotriene 1 and 2 receptors. *Proc Natl Acad Sci U S A* 2008; 105: 16695-16700.
10. Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. *New Engl J Med* 2002; 347: 1493-1499.
11. Steinke JW, Culp JA, Kropf E, Borish L. Modulation by aspirin of nuclear phospho-signal transducer and activator of transcription 6 expression: Possible role in therapeutic benefit associated with aspirin desensitization. *J Allergy Clin Immunol* 2009; 124: 724-730 e724.
12. Cahill KN, Bensko JC, Boyce JA, Laidlaw TM. Prostaglandin D₂: a dominant mediator of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2015; 135: 245-252.
13. Eastman JJ, Cavagnero KJ, Deconde AS, Kim AS, Karta MR, Broide DH, Zuraw BL, White AA, Christiansen SC, Doherty TA. Group 2 innate lymphoid cells are recruited to the nasal mucosa in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2017; 140: 101-108 e103.

14. Bankova LG, Lai J, Yoshimoto E, Boyce JA, Austen KF, Kanaoka Y, Barrett NA.
Leukotriene E4 elicits respiratory epithelial cell mucin release through the G-protein-coupled receptor, GPR99. *Proc Natl Acad Sci U S A* 2016; 113: 6242-6247.
15. Bankova LG, Boyce JA. A new spin on mast cells and cysteinyl leukotrienes: Leukotriene E4 activates mast cells in vivo. *J Allergy Clin Immunol* 2018; 142: 1056-1057.