

Paradigms and perspectives

Immunologic effects of aspirin desensitization and high-dose aspirin therapy in aspirin-exacerbated respiratory disease

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Respiratory reactions occurring minutes to hours following the ingestion of a COX-1 inhibitor represent the *sine qua non* of aspirin-exacerbated respiratory disease (AERD). Clinicians and researchers have capitalized on these unique respiratory reactions to COX-1 inhibitors to establish the diagnosis of AERD, differentiate the unique inflammatory state of AERD from aspirin-tolerant asthma (ATA) or chronic rhinosinusitis with nasal polypsis, and achieve a state of desensitization to initiate daily aspirin therapy. The clinical benefits of high-dose (325-1300 mg daily) aspirin therapy in AERD are well established and have been recently summarized by Stevens et al.¹ Here, we will review our current understanding of the immunologic impact of aspirin exposure during desensitization and daily high-dose therapy in AERD.

CHRONIC IMMUNOLOGIC DERANGEMENTS OF AERD

In the chronic disease state, AERD is classically characterized by 3 cardinal immunologic derangements: dysregulated lipid mediator production, chronic mast cell activation, and upper and lower respiratory tract type 2 (T2) inflammation.² Impairments in prostaglandin E₂ (PGE₂) production and/or signaling contribute to abundant cysteinyl leukotriene (cysLT) production and T2 cytokine production.³ Epithelial-derived cytokines, IL-33 and thymic stromal lymphopoietin (TSLP), and local immunoglobulin E, which are abundant in the nasal polyp tissue in AERD, cysLTs, and reduced PGE₂ level drive chronic mast cell activation with further production of cysLTs and PGD₂.⁴ PGD₂ in turn recruits effector cells expressing D prostanoid receptor, also known as chemoattractant receptor-homologous molecule expressed on T_H2 (CRTH2) cells, such

as eosinophils, basophils, group 2 innate lymphoid cells (ILC2s), and T_H2 cells, to the respiratory tract, whereas cysLTs increase mucus production. Both PGD₂ and cysLTs trigger bronchospasm. Together, these immunologic derangements result in a chronic disease state that is often characterized by severe asthma and aggressive nasal polyp regrowth.

ASPIRIN CHALLENGE AND DESENSITIZATION

Aspirin challenge involves exposure to increasing doses of aspirin until the onset of classical respiratory symptoms. Aspirin desensitization is the process by which we attain tolerance of aspirin in patients with AERD. Aspirin desensitization is achieved through the administration of higher doses of aspirin after the initial respiratory reaction occurs; remarkably, the aspirin-induced reactions subside, and higher doses are tolerated. Aspirin desensitization can be successfully achieved in most patients with AERD and allows for the initiation of daily aspirin therapy for AERD treatment or other medical indication. There are multiple published challenge and desensitization protocols, all of which are effective at achieving their diagnostic or therapeutic goal.¹ To maximize safety, cysLT₁ receptor antagonist pretreatment is used to attenuate the aspirin-induced decline in FEV₁. The collection of biospecimens during standardized aspirin challenge and/or desensitization protocols has been foundational to our current understanding of the unique immunology of AERD.

IMMUNOLOGIC EFFECTS OF ASPIRIN DESENSITIZATION

During a standardized aspirin challenge and/or desensitization protocol, the 3 cardinal immunologic derangements observed in the baseline AERD state are all enhanced (Fig 1, A). Aspirin-induced reactions typically occur at low doses (20-160 mg) that preferentially suppress COX-1. Impaired COX-2 expression and induction are reported in AERD, making patients more dependent on COX-1 activity to maintain PGE₂ production.⁴ In addition to serving as a modest bronchodilator, PGE₂ restrains 5-lipoxygenase (5-LO) phosphorylation and translocation to the nuclear membrane, thereby decreasing leukotriene production, and it serves as an inhibitor of mast cell activation.⁴ Pretreatment with inhaled PGE₂ abolished the aspirin-induced decline in FEV₁ and the systemic surge in cysLTs measured by the stable end metabolite urinary LTE₄ (uLTE₄), demonstrating the importance of PGE₂. Additionally, nasal polyp mast cells express greater amounts of COX-2 than COX-1.⁴ The early inhibition of COX-1, before COX-2 inhibition, is believed to allow massive mast cell PGD₂ production in the face of a COX inhibitor.⁴ Both local respiratory tract and systemic mast cell activation, as measured by histamine and tryptase levels, occur after exposure to aspirin.^{4,5}

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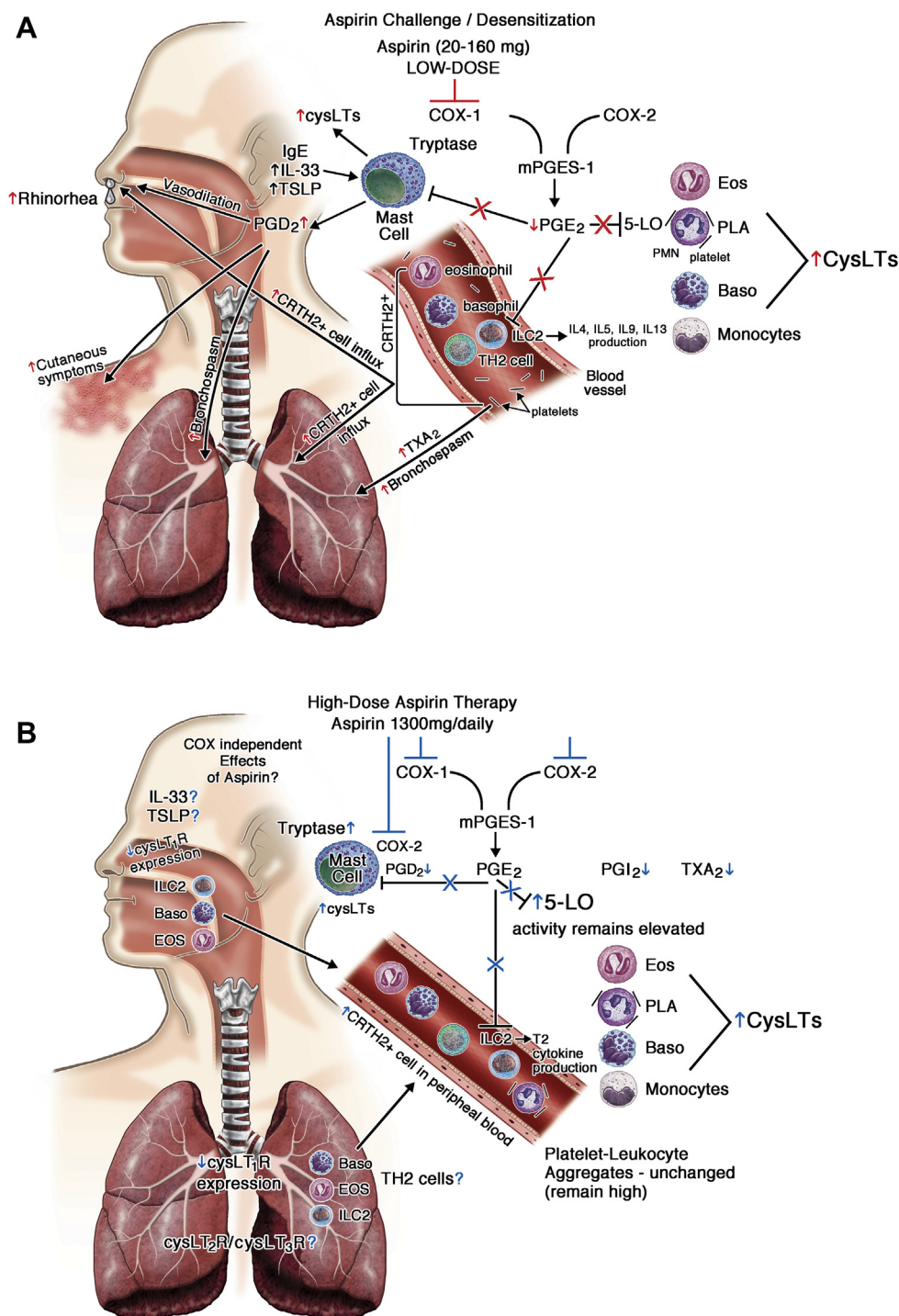


FIG 1. Current understanding of the immunologic effects of aspirin desensitization and high-dose aspirin therapy in patients with AERD. **A**, During aspirin challenge and/or desensitization, PGE₂ level declines, leading to enhanced mast cell activation, ILC2 cytokine production, and 5-LO activity and symptom onset. **B**, In subjects taking 1300 mg of aspirin daily, enhanced mast cell activation and 5-LO activity continue, whereas PGD₂ level and cysLT₁₋₃R expression decrease. cysLT₁₋₃R, Cysteinyl leukotriene 1-3 receptors; LT, leukotriene; mPGES-1, Microsomal prostaglandin E synthase-1; TX, thromboxane; PLA, platelet-leukocyte aggregates.

We reported that up to 50% of subjects with AERD experience systemic mast cell activation during an aspirin challenge and/or desensitization protocol.⁵ Systemic mast cell activation is associated with greater uLTE₄ and urinary PGD₂ metabolite production

and greater declines in FEV₁ during the 3 hours after reaction onset.⁵ Clinically, such patients report extrarespiratory symptoms involving the skin and gastrointestinal tract, both of which are associated with PGD₂ production, likely reflecting synergy

between IL-33 and TSLP and signaling at the DP1 receptor triggering vasodilation.⁴⁻⁶

Whereas mast cells are central to the chronic and acute inflammatory state in AERD, other inflammatory cells participate in aspirin-induced reactions and contribute to cysLT generation. Patients with AERD have increased circulating and tissue-resident platelet-leukocyte aggregates (PLAs) in the chronic disease state. Platelets contain the LTC₄ synthase required to convert LTA₄ into cysLTs and produce the potent bronchoconstrictor thromboxane A₂ when activated. When bound to neutrophils, which lack LTC₄ synthase but contain the 5-LO, platelets provide yet another unique source of cysLTs. The decline in PGE₂ and loss of restraint on 5-LO activity is anticipated to affect PLAs and enhance cysLT generation. Laidlaw et al demonstrated that aspirin exposure does not significantly alter peripheral blood PLA numbers or platelet activation state.⁷ However, they identified a subset of patients with a higher level of baseline PLAs who when pretreated with the platelet activation inhibitor prasugrel, demonstrated reduced uLTE₄ and urinary PGD₂ metabolite production, no increase in plasma tryptase level, and no reaction to aspirin.⁷ This supports platelet activation, at least in some patients, is contributing to the inflammatory state triggered by aspirin.

Mediator production from mast cells, specifically PGD₂, is believed to contribute to an acute influx of inflammatory cells into the respiratory tissue. Studies have demonstrated the efflux of CRTH2⁺ eosinophils and ILC2 from the bloodstream and the influx of CRTH2⁺ ILC2s into the nasal mucosa within hours of reaction onset.³ Studies with CRTH2 antagonists, which have not yet been performed in subjects with AERD, are required to confirm this mechanism.

The respiratory symptoms triggered by COX-1 inhibition classically peak and wane over a period of 3 hours, even without intervention. Once symptoms have subsided, higher doses of aspirin are generally tolerated without further respiratory symptoms, signaling that desensitization has been achieved.

IMMUNOLOGIC EFFECTS OF HIGH-DOSE ASPIRIN THERAPY

As daily high-dose aspirin therapy provides clinical benefit,¹ the immunologic changes in patients undergoing high-dose aspirin therapy may at first seem counterintuitive (Fig 1, B). Two studies assessed the impact of 8 weeks of aspirin in a dose of 1300 mg daily in patients with AERD,^{2,6} with one of these studies including important information from a cohort of patients with ATA who were also exposed to high-dose aspirin.² High-dose aspirin inhibits COX products, including PGE₂, PGD₂, prostacyclin, and thromboxane A₂ in subjects with AERD.⁶ Subjects with ATA demonstrate no appreciable change in systemic PGE₂ metabolite levels, whereas systemic PGD₂ metabolites decrease in subjects taking aspirin in a dose of 1300 mg daily.² The inability of subjects to maintain PGE₂ levels when taking high-dose aspirin in AERD highlights the fundamental difference between AERD and aspirin-tolerant T2 inflammation and further cements the critical role of PGE₂ as a key anti-inflammatory mediator in the respiratory tract. With the decrease in PGE₂ level, it is not at all surprising that we observe a concomitant rise in cysLT levels and increased mast cell activation, as assessed by serum tryptase level in subjects taking high-dose aspirin.² Circulating PLAs, a possible

source of increased cysLTs, are unchanged by high-dose aspirin. What is surprising is the clinical benefit derived from high-dose aspirin despite enhanced cysLT generation, which has been reported even after 52-weeks of aspirin therapy,⁸ and ongoing mast cell activation. Sousa et al observed that cysLT₁ receptor expression on nasal biopsy specimens decreases by 2 weeks of receiving daily aspirin therapy,⁹ supporting reduced end-organ reactivity to cysLTs as one mechanism by which higher cysLT production is tolerated. Additionally, aspirin has been shown to inhibit STAT6, a key transcription factor involved in T2 inflammation, and reduce sputum IL-4 levels after 6 months of high-dose aspirin therapy.¹⁰

Reductions in PGD₂ levels in subjects receiving high-dose aspirin therapy also contribute to clinical benefit. A decline in tissue PGD₂ level decreases the recruitment of CRTH2⁺ cells into the respiratory tract. We demonstrated a rise in blood eosinophil and basophil counts without a change in CRTH2⁺ blood cells at 8 weeks of high-dose aspirin.² PGD₂ is also a known driver of IL-4, IL-5, IL-9, and IL-13 cytokine production from ILC2s.³ The decline in PGD₂ may also reduce the capacity of remaining tissue-resident ILC2s to promote T2 inflammation. This lends further credence to the potential therapeutic benefit of suppressing PGD₂ signaling with selective CRTH2⁺ antagonists. However, PGD₂ is not the only eicosanoid to regulate ILC2 activation (recently summarized elsewhere³). We still lack a comprehensive understanding of the impact of high-dose aspirin therapy on the balance between anti-inflammatory (PGE₂ and prostacyclin) and proinflammatory (PGD₂ and cysLTs) eicosanoids in the respiratory tract.

SUMMARY AND FUTURE DIRECTIONS FOR RESEARCH AND TREATMENT

Standardized aspirin challenge and desensitization protocols and high-dose aspirin therapy provide an *in vivo* snapshot of eicosanoid regulation of respiratory tract T2 inflammation. Selective suppression of PGD₂ production and/or signaling is likely to be beneficial in patients with AERD, although this has not been studied. We and others have reported that some patients with AERD fail to tolerate aspirin desensitization and/or high-dose aspirin therapy owing to inflammatory side effects.⁶ The significant rise in mast cell activation and cysLT generation resulting from a loss of PGE₂ signaling supports the idea that abundant, unchecked mast cell activation may be responsible. Would direct inhibition of mast cells abolish aspirin-induced reactions and provide clinical benefit in AERD? If an appropriately safe and selective mast cell inhibitor were made available, I would start here. What happens to cysLT_{3R} expression, the recently described LTE₄ receptor, in the face of abundant LTE₄? Why does aspirin but not other reversible COX inhibitors provide clinical benefit? Are IL-33 and TSLP affected by acute or chronic aspirin exposure? Questions remain, and future research is likely to yield mechanistic insights into both aspirin-intolerant and aspirin-tolerant T2 inflammation.

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