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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 cyclooxygenase (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, to differentiate the unique inflammatory state of AERD from aspirin-tolerant asthma or chronic rhinosinusitis with nasal polyposis, and to 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 and colleagues(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 three cardinal immunologic derangements: dysregulated lipid mediator production, chronic mast cell activation, and upper and lower respiratory tract type (T)2 inflammation(2). Impairments in prostaglandin (PG)E2 production and/or signaling contribute to abundant cysteinyi leukotriene (cysLT) production and T2 cytokine production(3). Epithelial derived cytokines, interleukin (IL)-33 and thymic stromal lymphopoietin (TSLP), and local immunoglobulin E, abundant in the nasal polyp tissue in AERD, cysLTs, and reduced PGE2 drive chronic mast cell activation with further production of cysLTs and PGD2(4). PGD2 in turn recruits effector cells expressing D prostanoid receptor (DP)2, also known as CRTH2, such as eosinophils, basophils, group 2 innate lymphoid cells (ILC2) and T-helper type 2 (Th2) cells to the respiratory tract, while cysLTs increase mucus production. Both PGD2 and cysLTs trigger bronchospasm. Together these immunologic derangements result in a chronic disease state often characterized by severe asthma and aggressive nasal polyp regrowth.

Aspirin Challenge and Desensitization

An 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/desensitization protocols, all of which are effective at achieving their diagnostic or therapeutic goal(1). To maximize safety, cysLT1(R) receptor antagonist pretreatment is used to attenuate the aspirin-induced decline in forced expiratory volume in one second (FEV1). The collection of biospecimens during standardized aspirin challenge/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/desensitization protocol, the three cardinal immunologic derangements observed in the baseline AERD state are all enhanced (Figure 1a). Aspirin-induced reactions typically occur at low doses (20-160 mg) which 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). PGE2, in addition to serving as a modest bronchodilator, restraints 5-lipoxygenase (LO) phosphorylation and translocation to the
nuclear membrane thereby decreasing leukotriene production, and 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
(u)LTE₄, 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, occur after exposure to aspirin(4, 5). We reported that up to 50% of
subjects with AERD experience systemic mast cell activation during an aspirin
challenge/desensitization protocol.(5). Systemic mast cell activation is associated with greater
uLTE₄ and uPGD₂ metabolite production and greater declines in FEV₁ during the 3 hours after
reaction onset.(5). Clinically, such patients report extra-respiratory 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).

While 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 (PLA) in the chronic disease state. Platelets contain LTC₄ synthase required to
convert LTA₄ into cysLTs and produce the potent bronchoconstrictor thromboxane (TX)A₂ when
activated. Platelets when bound to neutrophils, which lack LTC₄ synthase but contain the 5-LO,
provide yet another unique source of cysLTs. The decline in PGE₂ and loss of restraint on 5-LO
activity is anticipated to impact PLAs and enhance cysLT generation. Laidlaw and colleagues
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 higher baseline
PLA who, when pretreated with the platelet activation inhibitor prasugrel, demonstrated reduced
uLTE₄, and uPGD₂ metabolite production, no increase in plasma tryptase, and no reaction to
aspirin.(7). This supports platelet activation, at least in some, 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 out of the blood stream and the influx of CRTH2+ ILC2 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 subside, higher doses of aspirin
are generally tolerated without further respiratory symptoms signaling desensitization has been
achieved.

Immunologic Effects of High-dose Aspirin Therapy

As daily high-dose aspirin therapy provides clinical benefit(1), the immunologic changes on
high-dose aspirin therapy may at first seem counter intuitive (Figure 1b). Two studies assessed
the impact of 8-weeks of aspirin 1300 mg daily in patients with AERD(2, 6), one included
important information from a cohort with aspirin-tolerant asthma (ATA) also exposed to high-
dose aspirin(2). High-dose aspirin inhibits COX products including PGE₂, PGD₂, PGI₂, and TXA₂
in subjects with AERD(6). Subjects with ATA demonstrate no appreciable change in systemic
PGE\(_2\) metabolite levels while systemic PGD\(_2\) metabolites decrease on aspirin 1300 mg daily(2). The inability to maintain PGE\(_2\) levels on high-dose aspirin in AERD highlights the fundamental difference between AERD and aspirin-tolerant T2 inflammation and further cements the critical role of PGE\(_2\) as a key anti-inflammatory mediator in the respiratory tract. With the decrease in PGE\(_2\), 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 on high-dose aspirin(2). Circulating PLA, 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 and colleagues observed that cysLT\(_1\)R expression on nasal biopsies decreases by 2 weeks on 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 PGD\(_2\) on high-dose aspirin therapy also contribute to clinical benefit. A decline in tissue PGD\(_2\) decreases the recruitment of CRTH2+ cells into the respiratory tract. We demonstrated a rise in blood eosinophils and basophils without a change in CRTH2- blood cells at 8-weeks on high-dose aspirin(2). PGD\(_2\) is also a known driver of IL-4, IL-5, IL-9, and IL-13 cytokine production from ILC2(3). The decline in PGD\(_2\) may also reduce the capacity of remaining tissue resident ILC2 to promote T2 inflammation. This lends further credence to the potential therapeutic benefit of suppressing PGD\(_2\) signaling with selective CRTH2+ antagonists. However, PGD\(_2\) is not the only eicosanoid to regulate ILC2 activation (recently summarized elsewhere)(3). We still lack a comprehensive understanding of the impact of high-dose aspirin therapy on the balance between anti-inflammatory (PGE\(_2\) and PGI\(_2\)) and proinflammatory eicosanoids (PGD\(_2\) and cysLTs) in the respiratory tract.

**Summary and Future Directions for Research and Treatment**

Standardized aspirin challenge/desensitization protocols and high-dose aspirin therapy provide an in vivo snapshot of eicosanoid regulation of respiratory tract T2 inflammation. Selective suppression of PGD\(_2\) production and/or signaling is likely to be beneficial in AERD although this has not been studied. We and others have reported some patients with AERD fail to tolerate aspirin desensitization and/or high-dose aspirin therapy due to inflammatory side-effects(6). The significant rise in mast cell activation and cysLT generation resulting from a loss of PGE\(_2\) signaling supports 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 was made available, I would start here. What happens to cysLT\(_1\)R expression, the recently described LTE\(_4\) receptor, in the face of abundant LTE\(_4\)? Why does aspirin versus other reversible COX inhibitors provide clinical benefit? Are IL-33 and TSLP impacted 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.

References:


**Figure Legend:**

Figure 1. Current understanding of the immunologic effects of aspirin-desensitization and high-dose aspirin therapy in patients with aspirin-exacerbated respiratory disease. A) During an aspirin challenge/desensitization prostaglandin E$_2$ declines leading to enhanced mast cell activation, type 2 innate lymphoid cell cytokine production, and 5-lipoxygenase activity and symptom onset. B) On 1300 mg of aspirin daily, enhanced mast cell activation and 5-lipoxygenase activity continues while PGD$_2$ levels and cysLT$_1$R expression decreases. COX – cyclooxygenase, mPGES-1 – microsomal prostaglandin E synthase-1, PG – prostaglandin, 5-LO – 5-lipoxygenase, PLA – platelet-leukocyte aggregate, LT – leukotriene, TX – thromboxane, CRTH2 - chemoattractant receptor-homologous molecule expressed on T-helper type 2, IL – interleukin, T$_{H}$2 – t helper type 2, ILC2 – group 2 innate lymphoid cell, TLSP - thymic stromal lymphopoietin, cysLT$_{1-3}$ R – cysteinyi leukotriene 1-3 receptors.