Mechanisms of Benefit with Aspirin Therapy in Aspirin-Exacerbated Respiratory Disease

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KEYWORDS

- Aspirin-exacerbated respiratory disease (AERD) • Aspirin desensitization
- Mechanisms of action • Cysteinyl leukotrienes (CysLTs) • Cytokines
- Interleukin 4 (IL-4) • Signal transducer and activator of transcription 6 (STAT6)
- Prostaglandin D2

KEY POINTS

- Aspirin-exacerbated respiratory disease (AERD) is characterized by severe, persistent asthma, hyperplastic eosinophilic sinusitis with nasal polyps, and intolerance to aspirin and other nonsteroidal anti-inflammatory drugs.
- Aspirin desensitization is an effective therapeutic option in carefully selected patients; however, the mechanisms behind the effects of aspirin desensitization remain poorly understood.
- AERD is associated with an overexpression of cysteinyl leukotrienes (CysLTs), with marked upregulation of CysLT receptors.
- Despite increased knowledge about the pathophysiology underlying AERD, the mechanisms behind the therapeutic effects of aspirin desensitization remain poorly understood.
- Recent studies suggest that the clinical benefits of aspirin desensitization may occur through direct inhibition of tyrosine kinases and the signal transducer and activator of transcription 6 pathway, with resultant inhibition of interleukin 4 production.
- A reduction in prostaglandin D2, as a consequence of aspirin desensitization, may also produce clinical benefit in AERD by precluding recruitment of PGD2 responsive effector cells to the airways.

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INTRODUCTION

Aspirin was first synthesized by Felix Hoffman in 1897 and was marketed by Bayer as an anti-inflammatory drug in 1899.[1] Idiosyncratic reactions to aspirin were reported shortly after the drug's development, although Widal and colleagues[2] was the first to describe aspirin challenges and desensitization for patients with the syndrome of asthma, nasal polyposis, and aspirin intolerance in 1922. Later, following works by Samter and Beers,[3] the condition was termed Samter triad because of the association of these 3 overlapping conditions, although aspirin-exacerbated respiratory disease (AERD) is now the preferred nomenclature. Stevenson and colleagues[4] reported the successful treatment of AERD with aspirin desensitization followed by daily aspirin therapy. Their study demonstrated significant clinical improvement in nasal symptoms and requirement for nasal steroids following aspirin desensitization.[5] Symptom improvement in AERD has been reported to occur as early as 4 weeks after initiation of aspirin therapy, and long-term benefits include considerable reductions in the number of sinus infections and surgeries, hospitalizations for asthma, and use of systemic steroids.[6,7] Despite these data, which support the clinical benefit, the mechanisms of aspirin therapy remain the least understood aspect of the disease.

Central to AERD is the dysregulation of endogenous inflammatory and anti-inflammatory mediators produced from the metabolism of arachidonic acid (also known as eicosatetraenoic acid).[8] Abnormalities in these eicosanoid mediators (including leukotrienes [LTs], prostaglandins [PGs], lipoxins [LXs], and their respective receptors) have all been implicated in the pathogenesis of AERD.[9] Evidence reveals that baseline expression of CysLTs is increased in patients with AERD and these levels further increase in response to cyclooxygenase-1 (COX-1) inhibitor challenge.[10–16] Concomitantly, in tissue mast cells (MC) and eosinophils, there is an increased expression of LTC_4 synthase (LTC_4 S), the rate limiting enzyme in CysLT synthesis.[17,18] $CysLT_1$ receptor expression is likewise elevated at baseline.[19] Reduction in the synthesis and under expression of PGE_2, an important inhibitor of 5-LO and thus leukotriene production, also contributes to AERD pathogenesis.[20]

Recent studies suggest that the AERD phenotype may result from a contribution of the cytokine interleukin 4 (IL-4), particularly in the presence of IFN-γ.[21–24] Aspirin desensitization and continued therapy leads to an immediate improvement in the dysregulation of arachidonic acid metabolism. During desensitization, urine LTE_4 ($uLTE_4$) levels initially increase following aspirin ingestion but subsequently decrease to basal levels with continued treatment.[25] $CysLT_1$ receptor expression is also decreased following desensitization.[19] Concomitantly, there is reduction of IL-4 induced expression of leukotrienes, which may occur through direct inhibition of the IL-4–activated signal transducer and activator of transcription 6 (STAT6) pathway.[21,24,26,27] A reduction in prostaglandin D_2, as a consequence of aspirin desensitization, may also produce clinical benefit in AERD by precluding recruitment of PGD_2 responsive effector cells to the airways.[28,29] These findings give insight into the mechanism of aspirin desensitization and are the subject of this review.

DESENSITIZATION EFFECTS ON PRODUCTS OF ARACHIDONIC ACID METABOLISM

LTE_4 is the most stable of the CysLTs and mediates many of the principal aspects of AERD, including bronchial constriction, hyperresponsiveness, eosinophilia, and increased vascular permeability.[30] Nasser and colleagues[25] studied the effects of aspirin desensitization on $uLTE_4$ concentrations in 9 patients with AERD. $uLTE_4$ levels