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A Review of Aspirin-exacerbated Respiratory Diseases and Immunological Efficacy of Aspirin Desensitization

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ABSTRACT

Aspirin-exacerbated respiratory disease (AERD) is a chronic inflammatory disease. It is defined by asthma, chronic rhinosinusitis with nasal polyposis, and a hypersensitivity reaction to aspirin or nonsteroidal anti-inflammatory drugs. Aspirin desensitization (AD) has been confirmed as an effective treatment to control AERD inflammation through the modulation of immune responses. We aimed to review AERD with an overview of the epidemiology, pathophysiology, and treatment. We also discussed the effect of AD on immunological markers involved in AERD pathogenesis. A search of electronic databases on AERD was performed. We included five randomized clinical trials (RCTs) on AD. We also searched databases for recent studies that investigated the effect of AD on the immunological mechanisms of AERD. RCTs have demonstrated the therapeutic effectiveness of AD on the patients' quality of life, asthma symptom score, inhaled and oral steroid use, forced expiratory volume in 1 sec (FEV1), and inflammatory mediators. The clinical benefits of AD can occur though the regulation of innate and adaptive immune responses that are involved in the pathogenesis of AERD. In addition to the valuable effects of AD in RCTs, some side effects such as gastrointestinal bleeding, asthma exacerbation, or rash have been reported that should be considered for reaching an optimal protocol for AD.

Keywords: Aspirin-exacerbated respiratory disease; Aspirin desensitization; Immune responses; Inflammations; Leukotrienes

INTRODUCTION

Aspirin exacerbated respiratory disease (AERD) or nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD) is known as an inflammatory condition created by an allergic reaction to aspirin and other cyclooxygenase (COX)-1 inhibitors.[1] AERD is characterized by asthma, chronic rhinosinusitis

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with nasal polyposis (CRSwNP), NSAID hypersensitivity rhinitis, excess mucus production, and eosinophilic inflammation.[1] Dysregulation of the enzymatic pathway that affects eicosanoid metabolism resulting in increased pro-inflammatory leukotrienes and decreased anti-inflammatory prostaglandins, is the most popular hypothesis about this inflammatory disease. However, not all aspects are well defined.

Methodology

A complete search in PubMed, Web of Science, Google Scholar, and Embase databases was performed by two researchers based on the keywords 'AERD', 'aspirin desensitization', 'immune mechanism', 'leukotrienes', 'biomarker', and 'cytokine'. All qualified studies published up to December 21, 2021, were included in this study. For clinical trial studies, we included 5 double-blind placebo-controlled studies investigating the effect of aspirin desensitization on AERD.

Epidemiology

AERD affects about 7% of patients with asthma, 14.9% with severe asthma, and 9.7% and 8.7% of patients with nasal polyps and chronic rhinosinusitis, respectively.[2,3] The disease generally develops during the fourth decade of life. Its diagnosis is often delayed, with a 10-year gap between the onset of symptoms and the age of diagnosis due to aspirin or NSAID-delayed reaction.[4]

Pathogenesis

The main mechanism in the pathogenesis of AERD is related to abnormalities in arachidonic acid metabolism pathways leading to the overproduction of leukotrienes with a concomitant decrease in prostaglandins.[5] There are two pathways for arachidonic acid metabolism: 5-lipoxygenase (5-LO) and the COX pathways. Cysteinyl-leukotrienes (CysLT), including leukotrienes C4, D4, and E4 (LTC4, LTD4, and LTE4), are produced by the 5-LO pathway from arachidonic acid, while prostacyclins, prostaglandins (PG), and thromboxanes (TX) are produced by the COX pathway.[2,6] In normal individuals, arachidonic acid is generally metabolized through the COX pathway, while in patients with AERD, this pathway is switched to the 5-LO pathway, leading to increased CysLT production and inflammation.

Cysteinyl Leukotrienes and Prostaglandins

CysLTs, including LTC4, LTD4, and LTE4, are produced primarily by basophils, mast cells, eosinophils, and platelets adhering to neutrophils. T cells, innate lymphoid cells (ILC), macrophages, granulocytes, platelets, airway epithelial cells, and smooth muscle cells receive leukotriene signals from their receptors, including CysLT1R, CysLT2R, and CysLT3R.[7] CysLT receptor engagement leads to mucin release, cytokine production, bronchoconstriction, and inflammation.[8]

On the other hand, PGE2 can attenuate the abovementioned symptoms by inhibiting the 5-LO pathway (CysLT synthesis). This inhibition occurs by PGE2/E prostanoid receptors 2 (EP2) signaling that increases the concentration of cAMP in the target cells and inhibits 5-LO localization to the nuclear envelope, which is an essential factor for LTA4 synthesis.[9,10] In addition to 5-LO inhibition, PGE2 reduces respiratory inflammation by a) inhibiting CD4 T cells to produce inflammatory cytokines such as tumor necrosis factor (TNF)-α, b) promoting alveolar macrophages to increase the expression of regulatory cytokines like interleukin (IL)-10, c) attenuating eosinophils migration, function, and cytokine production, and d) inhibiting mast cell degranulation, which decreases histamine and tryptase levels.[11-15]

It seems that in individuals without AERD, COX-1 inhibition and PGE2 reduction after aspirin ingestion can be compensated for by the COX-2 pathway. However, in AERD patients, COX-2 fails to produce enough PGH2 and PGE2 after COX-1 inhibition.[16] It has been shown that COX-2 expression in nasal polyp biopsies from patients with AERD is insufficient to produce an adequate level of PGE2 for inhibition of the 5-LO pathway and leukotriene production.[17] Some studies have shown that patients with AERD show a significant decrease in PGE2 levels in the peripheral blood cells and nasal tissue compared with healthy subjects, even without aspirin challenge.[8,18] These results confirm the protective role of PGE2 in AERD.

The decreased expression level of EP2 has been reported in AERD subjects compared to the healthy group.[19,20] AERD patients show decreased EP2 produced by leukocytes in the nasal mucosa compared to subjects without AERD.[21] Therefore, impaired PGE2 signaling also contributes to AERD pathogenesis.

Cytokines

Although CysLTs and PGE2 play an important role in AERD pathogenesis, recent studies have highlighted the role of thymic stromal lymphopoietin (TSLP) and IL-33 in AERD. These cytokines are expressed by airway epithelial cells and type 2 alveolar cells under CysLT stimulation. Evidence has shown that nasal polyp samples isolated from AERD patients express higher levels of TSLP and IL-33 than normal subjects.[22] IL-33 and TSLP are associated with CysLTs in a feed-forward mechanism, affecting ILC2s to release large amounts of type 2 inflammatory cytokines, including IL-5 and IL-13.[23] These cytokines influence mast cells to release tryptase, histamine, thromboxane B2 (TXB2), prostaglandin D2 (PGD2), and LTC4.[24] Histamine, PGD2, and TXB2 promote AERD symptoms and LTC4 increases IL-33 and TSLP concentration. Furthermore, IL-13 induces the expression of IL-33 in epithelial cells.[25] This feed-forward mechanism is associated with high production of pro-inflammatory leukotrienes, cytokines, and histamine. It leads to chronic inflammation and bronchoconstriction.[9]

Genetic Factors

AERD phenotypes are characterized by genetic variations in pathways involved in arachidonic acid metabolism, inflammation, and immune responses. It seems that genes like *LTC4S*, arachidonate 5-lipoxygenase (*ALOX5*), *CYSLTR1*, and *CYSLTR2*, which are involved in the signaling pathway of arachidonic acid metabolism, are the most important candidate genes that contribute to AERD pathogenesis.[26] The major histocompatibility complex (MHC) II locus, as the initiator of T cell function, has strong associations with AERD in several genetic investigations. To date, the most common genetic marker for AERD is HLADPB1*0301, associated with a higher prevalence of chronic rhinosinusitis.[27] A recent genetic association study by Esmaeilzadeh et al. showed that HLA-DQB1*0302, HLA-DRB1*04, and their related haplotypes are related to AERD predisposition, whereas HLA-DQB1*0301 and HLA-DRB1*011 had inverse associations with AERD.[28]

In addition to studies that identified predisposing genes involved in AERD pathogenesis, a number of pharmacogenetic studies have been performed to predict treatment responses in AERD patients. Candidate gene and genome-wide investigations revealed that *ALOX5*, *ALOX5AP*, *LTC4S30*, *CYSLTR1*, *CYSLTR2*, *ABCC1*, and *OATP2B1* genes are involved in antileukotriene responses.[26] One study identified HLADPB1*0301 to be associated with increased leukotriene receptor antagonists, while another identified HLA-DQB1*0302 as a genetic marker for favorable reactions to aspirin desensitization (AD).[28,29] Epigenetic modifications, such as histone protein modification and DNA methylation, also contribute to the regulation of many genes involved in AERD pathogenesis.[19] The development of noninvasive biomarker studies using genetic, epigenetic, and pharmacogenetic data can help improve AERD and asthma treatment.

AERD Treatment

The most important therapies for AERD include endoscopic sinus surgery (ESS), corticosteroids, leukotriene modifiers, biological agents, and AD.

Endoscopic Sinus Surgery

ESS can relieve symptoms in most AERD patients. However, it should be combined with postoperative treatments such as AD, corticosteroids, or biological agents to avoid recurrence. Patients who had undergone ESS showed a significant decrease in urinary LTE4, an increase in PGE2 levels, and less severe reactions to AD.[30,31]

Corticosteroids

Corticosteroids are used in different ways, including intranasal, oral, and inhaled corticosteroids. Intranasal corticosteroids can be considered the first treatment administered to patients with AERD as they can decrease new polyp formation, sinus inflammation, and rhinitis symptoms.[32] These medications can also prevent polyp relapse after ESS by inhibiting phospholipase A2 (PLA2) () , which involves releasing arachidonic acid from membrane phospholipids.[33] Oral and intranasal corticosteroids reduce the nasal polyp tissue and mucosal edema. Inhaled corticosteroids in connection with bronchodilator therapy and β2-agonists are preferable for asthma management in AERD.[34] This may be due to the fact that inhaled corticosteroids reduce the inflammatory response and the need for systemic treatment.

Leukotriene Modifiers

As the overproduction of CysLTs is the main pathological feature of AERD, using leukotriene modifiers can be a suitable treatment strategy.

Leukotriene modifiers can reduce inflammatory immune responses by a) blocking CysLT receptors as receptor antagonists and b) inhibiting 5-lipoxygenase.[35] CysLT receptor antagonists improve lung function and quality of life in AERD patients.[2]

Biological Agents

Biological agents such as monoclonal antibodies (mAbs) are usually designed and used to improve respiratory diseases in people with allergies and asthma; however, the results of mAb consumption in patients with AERD can indicate the benefits of biological agents in AERD.[36,37] omalizumab (anti-IgE mAb) is one the most important mAbs used in patients with asthma. This recombinant antibody works by inhibiting the interaction between IgE and its high-affinity receptor, FcεR. One study has reported the role of omalizumab in reducing CysLTs and prostaglandin F2 (PGF2) overproduction in AERD.[37] Since AERD is not an IgE-dependent disease, the benefits of such treatment for AERD remain challenging. As IL-5, IL-4, and IL-13cytokines have essential roles in AERD pathogenesis, mAbs that target these cytokines or their receptors can be suitable for AERD treatment and control of asthma and allergies. Mepolizumab, reslizumab, and benralizumab all are IL-5 antagonists, inhibiting eosinophil recruitment, activation, and survival.[38] IL-5 inhibition with mepolizumab could relieve the upper airway respiratory symptoms, such as anosmia and nasal congestion, and restrict asthma in subjects with AERD and severe asthma.[39] Reslizumab also reduces eosinophilic cationic protein levels, diminishes the eosinophil lysophospholipase gene expression and decreases peripheral eosinophilia in patients with AERD.[40] The overall effects of IL-4 and IL-13 are inhibited by dupilumab through IL-4α antagonist receptor blocking. Clinical research has shown that the use of dupilumab in AERD patients has been associated with a significant decrease in nasal polyp, Lund-Mackay, morning nasal congestion and obstruction scores, and an improvement in the University of Pennsylvania Smell Identification Test (UPSIT) scores.[41]

Aspirin Desensitization

Aspirin desensitization is the gold standard treatment for AERD patients. Induced resistance to aspirin and NSAID is the phenomenon in which the STAT6 pathway and leukotrienes production are inhibited by AD.[42] Therapeutic advantages of AD include reducing nasal polyp regrowth after ESS and occurrence of sinusitis and the need for systemic corticosteroid consumption.[43] Below, we have reviewed the randomized clinical trials (RCTs) that investigated AD in AERD patients.

A Review of Current RCTs for AD in Patients with AERD

Stevenson et al. first reported the therapeutic efficacy of AD for two aspirin-sensitive patients in 1980.[44] To test the hypothesis that AD, followed by daily ingestion of aspirin, can improve the clinical course of rhinosinusitis or asthma in aspirin-sensitive individuals, Stevenson et al. in 1984, conducted a double-blind crossover study for the first time to compare aspirin with placebo therapy.[45] During the months when patients received 1300 mg aspirin daily, half of the patients showed a significant clinical improvement in nasal symptoms and decreased need for nasal steroids. However, this study found no significant changes in lower respiratory tract symptoms, forced expiratory volume in 1 sec (FEV1), or anti-asthmatic medication use during aspirin treatment [46] Subsequently, numerous nonrandomized controlled trials demonstrated the therapeutic efficacy of AD.[46-50] These studies investigated the influence of AD on parameters such as the number of sinus infections per year, olfactory scores, nasal and asthma symptom scores, sinus operations, hospitalizations, and emergency room visits. However, the number of randomized double-blind placebo-controlled studies in this field is limited. To date, five double-blind placebo-controlled studies have been performed on the outcomes of AD for AERD. After that, Fruth et al. (2013) assessed the efficacy of low-dose AD in a double-blind and placebo-controlled clinical trial on patients with AERD.[46] Previous studies in this field were performed with varying maintenance doses of up to 1300 mg aspirin daily. They were associated with severe side effects, such as gastric pain and bleeding in some cases. These concerns led Fruth et al. to prospectively evaluate the desensitization protocol with low-dose AD. They enrolled 70 patients with AERD who had undergone sinus surgery with a maintenance dose of 100 mg daily. They found that AD with a maintenance dose of 100 mg daily improved the clinical complaints and the quality of life of individuals with AERD after 36 months without any side effects. However, they failed to significantly reduce nasal polyp relapse and polyposis scores. This might be related to the high dropout rate (55.7%) and low maintenance aspirin dose of 100 mg daily in this study.[46] Another double-blind, placebo-

controlled study in this field was carried out by S´wierczynska-Krepa et al.[51] In their study, 20 AERD patients were assigned to either an aspirin therapy group (maintenance dose of 624 mg for 6 months) or a placebo group to assess their clinical and immunological markers. They found that AD was associated with improved quality of life parameters, asthma symptoms, inhaled corticosteroids use, and peak nasal inspiratory flow in the aspirin therapy group compared to the placebo group. There were no changes in immunological markers, LTE4, 9α, or PGF2 levels after AD. Adverse gastrointestinal effects due to AD were observed in 5 patients in the aspirin group.[51] Esmaeilzadeh et al. designed a randomized double-blind placebo-controlled study to investigate the impact of AD with the maintenance dose of 625 mg daily on clinical and immunological markers of 34 patients with AERD.[47] In this study, AD was associated with improved quality of life, reduced symptoms, and higher FEV1 in the aspirin group compared to the placebo group. As previous studies revealed that interferon (IFN)-γ inflammatory cytokine and some anti-inflammatory cytokines like tumor growth factor (TGF)-β and IL-10 have a role in AERD pathogenesis, they aimed to quantify these cytokines to illustrate the mechanism of AD.[52] However, they failed to observe a significant difference between the two groups regarding the serum levels of these cytokines, neither at baseline nor at the end of the study. They suggested that these non-significant results might be related to the lack of cytokine expression assessment in the sinus and airway tissues of AERD patients that should be considered in future studies. The latest double-blind randomized clinical trial study in this field was designed by Mortazavi et al. in which 38 AERD patients were included and divided into two aspirin and placebo groups with a maintenance aspirin dose similar to that of Esmaeilzadeh et al.[47,53] This was the first study to evaluate IL-5 as an immunological marker involved in the pathogenesis of AERD. The study showed that AD could improve the quality of life of patients with AERD, relieve their symptoms, and decrease IL-5 levels and FEV1 scores.[53]

Despite the noticeable benefits of AD for AERD patients, it is not free of side effects. In some studies, up to 50% of patients leave AD due to its side effects, such as asthma exacerbation, gastrointestinal bleeding, or rash.[47,51,53] Considering the importance of such side effects in AD treatment, it seems essential to optimize clinical trials regarding the AD protocol, study population, randomization, and gene variability to reach better results for this treatment.

Effects of AD on Immunological Markers Involved in the AERD Pathogenesis

The exact cellular and molecular mechanisms that lead to improvement following AD are not fully understood. It has been demonstrated that AD modulates deregulated immune responses in AERD through decreased levels of pro-inflammatory CysLTs and their receptors, inhibition of Th2 activation, IL-4 production, and mast cell activation. Figure 1 illustrates the mechanisms of AERD pathogenesis and the inhibitory effects of AD on these immunological mechanisms.

In the following, we have summarized those immunologic and biological mediators important in AERD and, consequently, the effects of AD on these mediators. A list of relevant studies is summarized in Table 1.

Innate Immunity in AERD and AD

Mast Cells (MCs)

It has been shown that MCs play a critical role in the pathogenesis of AERD.[54] When activated during aspirin reactions, they release mediators such as CysLTs, PGD2, tryptase, histamine, and various chemokines and cytokines. These mediators promote inflammation in AERD by stimulating a network of immune cells involved in both acute and chronic inflammatory pathways such as epithelial, endothelial, stromal, and other immune cells.[55-57] LTE4 is one of the most important members of CysLTs, which mediates some critical features of AERD, such as increased bronchial constriction, vascular permeability, eosinophilia, and hyper-responsiveness. Measuring urinary leukotriene E4 (uLTE4) is a sensitive and noninvasive method of assaying total body cysteinyl leukotriene production and changes in cysteinyl leukotriene levels in specific microenvironments, such as the airways. Although several studies have highlighted the importance of LTE4 in AERD, this molecule has a relatively low affinity for the well-known CysLT receptors, namely, CysLT1 and CysLT2, suggesting that there might be a more specific CysLTER through which LTE4 signals.[58] In support of this hypothesis, Maekawa et al. have reported that in CysLT1R/CysLT2R double-deficient mice, intradermal injection of LTE4 leads to significant vascular leak.[59] These data need further confirmation in patients with AERD to identify a specific CysLTER.

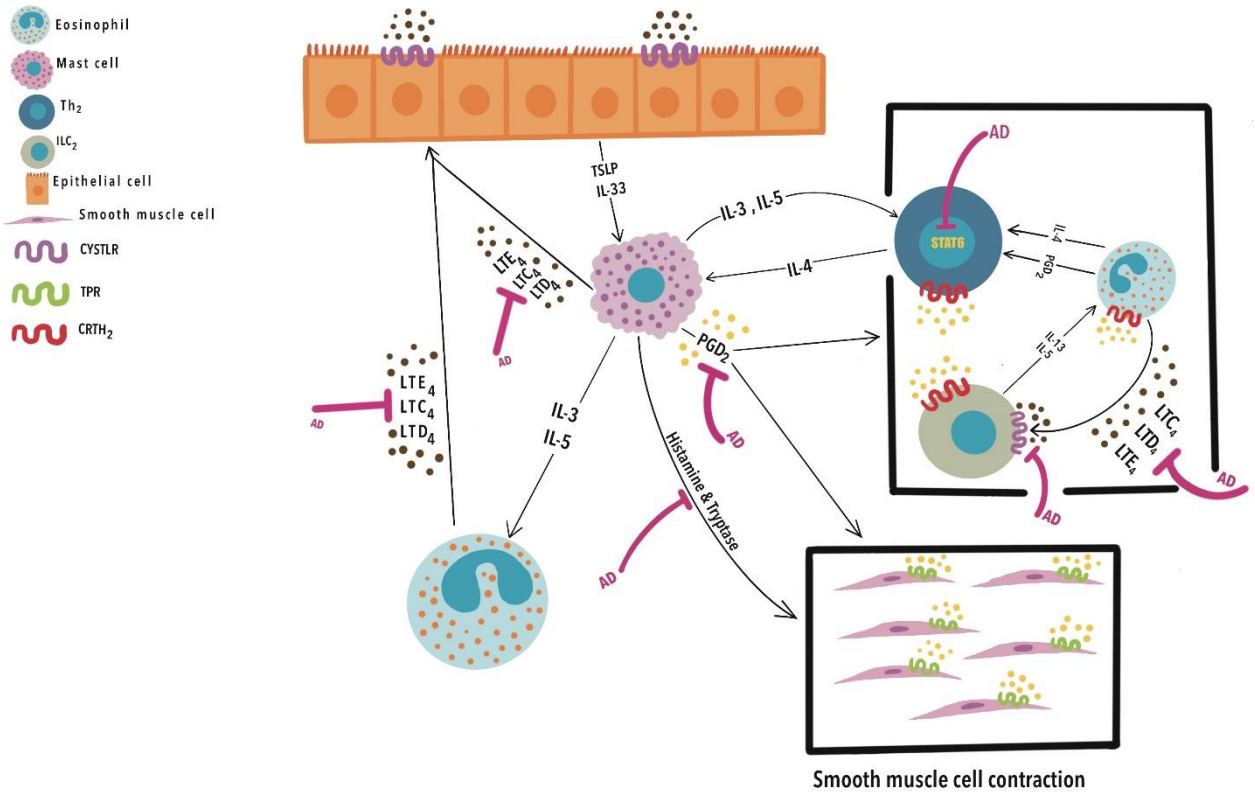

Figure 1. Immunological pathways in AERD and AD. Type 2 inflammation is the most important immune response in AERD. Overproduction of CysLTs, IL-33/TSLP, and PGD2 leading to the classical disease exacerbations, after Aspirin/NSAIDs administration. AD ameliorates AERD exacerbation through an inhibitory effect on these pathways. Abbreviations: ILC2, innate lymphoid cell; Th2, T-helper 2; CYSTLR, Cysteinyl leukotriene receptor; TPR, T prostanoid receptor; CRTH2, Chemoattractant receptor-homologous molecule expressed on TH2 cells; TSLP, thymic stromal lymphopoietin; LT, Leukotriene; PGD2, prostaglandin D2; AD, aspirin desensitization.

As different pathologic mediators such as CysLTs and PGD2 are produced by MCs, the benefits of AD can be partly attributed to the inhibition of MC degranulation and improvement of the arachidonic acid cascade within these cells. In the case of the effect of AD on CysLT, there is no consistency between data. Cahill et al. and Bobolea et al. found that AD did not affect the levels of urinary LTE4 or sputum LTC4.[55,60,61] Nasser et al. found that prior to aspirin desensitization, the first dose of aspirin administration led to a 7-fold increase in uLTE4 compared to the baseline level.[62] However, with the initiation and maintenance of therapy, this increase was only 2 folds, showing that AD led to less aspirin-induced LTE4 excretion in the urine.[62] In contrast, recently, Cahill et al. showed that the levels of urinary LTE4 increased in patients with AERD 8 weeks post high dose aspirin therapy.[61] The underlying causes for these discrepancies are not clear, and further controlled and detailed studies are needed to explore the exact fluctuations of CysLT in the process of AD.

Additionally, AD is associated with decreased expression of the CysLT1R and an approximate 20-fold decrease in sensitivity to inhaled LTE4.[63,64] The exact mechanisms of this effect are not clearly understood; however, it may be related to COX-independent mechanisms, including its ability to inhibit STAT6 signaling and prevent IL-4 production.[50,65,66]

Another beneficial mechanism of AD is its ability to decrease PGD2 inflammatory mediator, which is a potent chemotactic factor for T helper-2 (Th2) cells, innate helper lymphoid cells, basophils, and eosinophils, all of which can affect AERD severity through their mediators.[55, 60, 61,67] Cahill et al. demonstrated that those AERD patients who failed to tolerate AD over-produced

PGD2 compared to aspirin tolerant patients. Besides, they showed that regular aspirin therapy for 8 weeks resulted in a significant decline in urinary prostaglandin metabolite levels, suggesting reduced generation of these molecules in AERD patients undergoing therapeutic desensitization.[55,61] Besides, Bobolea et al. showed that 1 and 6 months after AD, inflammatory sputum PGD2 (sPGD2) decreased, whereas anti-inflammatory sPGE2 increased.[60] These findings highlight the importance of prostaglandins in AERD and AD and suggest PGD2 receptor antagonists as a new therapy for AERD.

All the abovementioned mechanisms, including decreased expression of CysLT1R, reduced sensitivity to LTE4 and production of PGD2, and increased level of sPGE2, are the beneficiary immune-mediated mechanisms of AD.

Table1. Summary of relevant studies that investigated the effects of AD on immunological markers.

Study (Reference) (year)	Number of Patients	Design	Intervention (AD protocol)	Findings
Katial et al.[50] (2010)	21 (AERD)	Clinical trial	-Oral desensitization to aspirin over 2 days - Daily ingestion of aspirin 650 mg twice daily	↓IL-4; ↓MMP9; ↑FLT3-L
Cahill et al.[55] (2015)	29 (AERD)	Prospective	-Started with 40 mg aspirin -Followed by dose increase (81 mg, 162 mg, 325mg) every 90 min	Unchanged PGD-M; ↓TX-M; ↑blood eosinophil and basophil levels; ↓uPGD-M
Bobolea et al.[60] (2018)	14 (AERD)	Prospective	650 mg during one month	↓PGD2; unchanged LTC4; unchanged LTC4/PGE2; ↑TSLP; ↑PGE2; ↑TSLP/PGD2
Cahill et al.[61] (2019)	42 AERD 15 ATA	Prospective	1300 mg	↓nasal symptoms; ↓uPGE-M; ↑uLTE4 ↑uPGD2; ↓TX-M; ↑blood eosinophil and basophil; ↑exhaled NO and plasma tryptase
Nasser et al.[62] (1995)	9 (ASA)	Prospective	600 mg	↓FEV1; ↓uLTE4
Sousa et al.[63] (2002)	22 (AERD) 12 (non-AERD)	Clinical trial	8 mg intranasal lysine aspirin	↓inflammatory cells expressing CysLTR1
Arm et al.[64] (1989)	5 (AIA); 15 (non-AIA)	Comparative	600 mg	↑LTE4; ↓Histamine

AERD, aspirin-exacerbated respiratory disease; AD, aspirin desensitization; IL, interleukin; MMP, matrix metallopeptidase; FLT3-L, fms-related tyrosine kinase 3-ligand; PGD-M, prostaglandin D-metabolite; TX-M, thromboxane-metabolite; LTC, leukotriene C; PGE, prostaglandin E; TSLP, thymic stromal lymphopoietin; u, urinary; NO, nitric oxide; FEV, forced expiratory volume; CysLTR, Cysteinyl leukotriene receptor; mg, milligram; ATA, aspirin-tolerant asthmatic; ASA, aspirin-sensitive asthma; AIA:aspirin-induced asthma; ↑, increase; ↓, decrease

Eosinophils

In addition to mast cells, eosinophils are another crucial innate immune population in AERD.[68] Eosinophils are one of the main innate immune cells in patients with AERD. Sladek et al. reported increased eosinophils and eosinophil cationic protein levels in the bronchoalveolar lavage fluid and nasal tissue biopsies of patients with AERD.[69] Considering AD and eosinophil's cellular changes, it has been shown that aspirin maintenance therapy is associated with a high number of circulating eosinophils in the peripheral blood, which suggests that these inflammatory cells are no longer recruited into the affected tissue to exacerbate the inflammatory milieu, thus alleviating the respiratory parameters.[61]

Innate Lymphoid Type 2 Cells (ILC2s)

Several researchers have recently been interested in the role of ILC2s in AERD patients.[70,71] AERD tissue samples consist of high levels of mediators such as PGD2, CysLTs, and IL-33, which can act both as ILC2 recruiters and activators.[55,72-75] During AERD reactions, ILC2s are recruited to the nasal mucosa and reduced in the peripheral blood of AERD patients. The increased ILC2 levels in the nasal mucosa correlate with elevated production of prostaglandins, leukotrienes, and symptom severity scores of the disease.[71] These findings emphasize that ILC2s are important players in the context of AERD. However, several other experiments are needed to precisely define the role of ILC2 molecular mediators in AERD and how AD therapy can affect this cell population.

Adaptive Immunity in AERD and AD

T Cells and Their Cytokines

Until now, a few studies have been conducted on changes in adaptive immune responses during the AD procedure. In this regard, a study found no significant difference in the percentage of CD4 T cells or their cytokines such as IL-4, IL-2, and IFN-γ in patients suffering from AERD one month after starting AD compared with the baseline.[76] However, this finding cannot exclude the long-term effects of AD procedure on T cells and their mediators.

The effector responses during AD procedures diminish and can be attributed to immune regulatory mechanisms such as regulatory cells or cytokines. It has been suggested that immune regulatory cytokines such as IL-10 and IL-35 are essential in desensitization procedures for several drugs.[77,78] In the case of AD in AERD patients, Aksu et al. showed that intracellular expression of IL-10 in CD4 T cells declined after 1 month of desensitization.[79] Decreased IL-10 in T cells may suggest that these cells secrete their anti-inflammatory cytokines to control effector immune mechanisms. As there are few data on the importance of regulatory cells such as Treg, Tr35, and Breg cells in the context of AD, it is highly recommended that future studies evaluate the significance of these regulatory subsets and their anti-inflammatory mediators in the context of AERD and AD.

Th2 cells are one of the most important adaptive immune cells that play a role in AERD and AD through their mediators and interactions with MCs.[80] It has been suggested that AD followed by a daily maintenance dose reduces activation of tyrosine kinase and STAT6 phosphorylation, decreases the production of IL-4, and reduces expression of the CysLT1R, ultimately leading to the attenuation of airway inflammation and clinical improvement in the context of AERD.[63,65,66]

One of the key immune cells in this process is the Th2 subpopulation. Th2 cells and PGD2 can have reciprocal effects in the context of AD. PGD2 is a dominant chemotherapeutic factor for Th2 cells; therefore, an AD-mediated decrease in inflammatory PGD2 can lead to diminished recruitment of Th2 cells into inflamed tissues and enhanced clinical parameters seen in the AD process.[55,60,67] We propose that further studies are needed to define the correlation between these immune cells and inflammatory or anti-inflammatory mediators in the context of AERD and AD.

In conclusion, AERD is a chronic inflammatory condition characterized by asthma, chronic rhinosinusitis with nasal polyposis, and intolerance to aspirin and other NSAIDs that preferentially inhibit COX-1. The disease is associated with increased inflammatory responses due to dysregulation of multiple enzymes that influence eicosanoid metabolism. AD is introduced as an effective tool for AERD treatment by RCTs. It improves some AERD clinical features such as asthma symptoms, quality of life, inhaled and oral corticosteroids use, peak nasal respiratory flow, and FEV1. The exact mechanisms behind the beneficial effects of AD remain poorly understood. Recent studies have suggested that it may be related to the modulation of innate and adaptive immune cell dysregulation in AERD. Besides the benefits of AD, this treatment may be associated with side effects such as gastrointestinal bleeding, asthma exacerbation, or rash in some cases that cause patients to leave aspirin desensitization experiments. Therefore, further studies need to be conducted to reach an optimized AD protocol.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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