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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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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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