



Aspirin exacerbated respiratory disease (AERD): molecular and cellular diagnostic & prognostic approaches

Habib Hybar¹ · Najmaldin Saki² · Mohsen Maleknia³ · Mana Moghaddasi⁴ · Armin Bordbar⁵ · Maliheh Naghavi⁶

Received: 15 December 2020 / Accepted: 16 February 2021
© The Author(s), under exclusive licence to Springer Nature B.V. part of Springer Nature 2021

Abstract

Aspirin-exacerbated respiratory disease (AERD) is characterized by immune cells dysfunction. This study aimed to investigate the molecular mechanisms involved in AERD pathogenesis. Relevant literatures were identified by a PubMed search (2005–2019) of english language papers using the terms “Aspirin-exacerbated respiratory disease”, “Allergic inflammation”, “molecular mechanism” and “mutation”. According to the significant role of inflammation in AERD development, ILC-2 is known as the most important cell in disease progression. ILC-2 produces cytokines that induce allergic reactions and also cause lipid mediators production, which activates mast cells and basophils, ultimately. Finally, Monoclonal antibody and Aspirin desensitization in patients can be a useful treatment strategy for prevention and treatment.

Keywords Aspirin-exacerbated respiratory disease · Allergic inflammation · Molecular mechanism · Mutation

Abbreviations

AERD Aspirin Exacerbated Respiratory Disease
NSAIDS Nonsteroidal anti-inflammatory drugs
BAG-1 BCL-2 associated athanogenet
TLR Toll Like Receptor

Introduction

Aspirin-exacerbated respiratory disease (AERD) is an inflammatory disorder, which is caused by allergy to non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin

[1]; it is acquired, and most often higher prevalence occurs in individuals over the age of thirty. The main pathogenesis is related to the cyclooxygenase-1 (COX-1) inhibition, which is an involved enzyme in the prostaglandins production [1, 2]. So far, the genetic factors that predispose people to AERD have not been identified. However, many environmental and acquired factors contributed to disease have been known. The main mechanisms of the disease are autoimmune reactions and chronic viral infections [3].

The clinical symptoms of the disease are very variable; it is very hard in some people, and sometimes no clinical signs are observed for a long time. In contrast, respiratory

✉ Maliheh Naghavi
naghavi@zums.ac.ir

Habib Hybar
takamoolsk@yahoo.com

Najmaldin Saki
najmaldinsaki@gmail.com

Mohsen Maleknia
maleknia.m94@gmail.com

Mana Moghaddasi
Moghaddasi1368@gmail.com

Armin Bordbar
Dr.bordbar@zums.ac.ir

¹ Atherosclerosis Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

² Thalassemia and Hemoglobinopathy Research Center, Research Institute of Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

³ Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

⁴ Department of Biology, Payame Noor University (PUN), Tehran, Iran

⁵ Department of Cardiology, Musavi Hospital, School of Medicine, Zanjan University of Medical Science, Zanjan, Iran

⁶ Department of Pathology, Vali-E-Asr Hospital, School of Medicine, Zanjan University of Medical Science, Zanjan, Iran

disorders such as cough and wheezing are found in some other patients [4]. Also, the duration of symptoms and their stability varies significantly depending on the type of cell activation in the patient's body, which can be due to the causative agents of basophils, mast cells or platelets [5]. Therefore, in this study, we investigated the molecular and pathological mechanisms of AERD from a prognostic and diagnostic perspective.

Pathophysiology of AERD

Blood cells

The cause of AERD pathogenesis is the use of NSAIDs, which stimulates the reactive cells including platelets, basophils, mast cells and eosinophils [6]. On the other hand, the function of Th1 inflammatory cells, which produce inflammatory cytokines, is impaired. Therefore, the mechanisms that block the inhibitory functions of reactive cells in IFN- γ production can form a therapeutic strategy, which could be a diagnostic and prognostic approach for AERD disease [7, 8].

Platelet

Platelets are one of the main components of the homeostasis system, which play an essential role in clot formation and bleeding prevention. Platelets initiate coagulation cascades by generating stimuli and inducing signaling pathways [9]. In some cases, such as AERD, platelet activation leads to the disease and its clinical complications. The platelet count in AERD patients is higher than normal individuals. In the pulmonary tissues, the accumulation of platelets is very high, lonely or in contact with leukocytes (through some factors such as P-selectin). Leukotrienes are one of the pre-inflammatory factors, which release during the platelet activation and activate the metabolism of arachidonic acid.

Leukotriene C4 (LTC4) is one of the platelet leukotrienes; its cycLT2R is present on many cells, including platelets [10, 11]. LTC4 autocrine binding to cycLT2R on platelets release High mobility group box 1 (HMGB1) (one of the stimuli of the innate immune system) from platelets. The HMGB1 receptor includes TLR4 and receptor for advanced glycation end product (RAGE), which are expressed on the lung and platelet, respectively. Therefore, HMGB1 binding to RAGE, stimulates cells and epithelial tissues of the lungs to secrete cytokines such as IL-25, IL-33, IL-13 and IL-5, which activate basophils, eosinophils and mucus secretion [10].

Thromboxane A2 (TXA2) is another platelet-mediated inflammatory that activates platelets by binding to its T-prostanoid receptor (TP). TP is one of the main factors in the binding of platelets and leukocytes; also, Intercellular Adhesion Molecule 1 (ICAM-1) expression increases the

movement of leukocytes toward endothelial cells and tissues [12, 13]. P2Y12 is another platelet surface receptor, which release platelet micro particle (MP) by interacting with ADP.

The results of studies have shown that the use of P2Y12 antagonist (such as Clopidogrel) has no effects on the AERD treatment; it does not prevent the progression and worsening of the disease. But another study found that the use of the P2Y12 antagonist had different effects on the platelet function, depending on the involved Toll Like Receptors (TLRs).

It has been demonstrated that platelet-secreted MPs, which activate TLR2 at platelet surfaces reduce the production of inflammatory cytokines such as IL-17 and IFN-G; platelet MPs induce cytokine production by activating TLR4 [14, 15]. Another study showed that a group of T-regulatory cells (Treg) produces inflammatory cytokines in the event of inflammation; however, the secretion of some MPs inhibits the production of inflammatory cytokines by Tregs [16]. Platelet P-selectin binding with leukocyte P-selectin glycoprotein ligand-1 (PSGL-1) can activate the PKC-AKT-MAPK path. According to this fact, activation of the AKT prevents ICAM-1 expression on endothelial cells and tissues and reduces the chemotaxis of immune cells to the tissues; it also prevents the production of IFN-G [12]. AKT targeting can be done in AERD patients with desensitization and disease severity reduction.

Eosinophil

Eosinophils are one of the main causes of allergic inflammation, which are transmitted to the inflammation site by chemotactic substances release. Eosinophils complicate the pathogenesis mechanism of AERD by producing lipid mediators such as leukotrienes [17, 18]. Arachidonic acid metabolism is done by eosinophils; although the involved enzymes in the cited process are known, but their molecular mechanism and pathogenesis have not been identified fully, yet. Therefore, the identification of these pathways can provide an appropriate treatment strategy to prevent the activation of eosinophils in AERD patients [17].

In addition, eosinophils have been shown to cause chronic rhino sinusitis (CRS) with or without nasal polyps (NPs). CRS has been shown to be similar to AERD in some symptoms. Eosinophils increase the production of cytokines including IL-4, IL-5 and IL-13, by inducing HMGB1 secretion. In addition to IGE production increment, these cytokines increase TLR-9 expression. TLR-9 ultimately increases cytokine production by activating the NF- κ B pathway [19]. furthermore, the NF- κ B pathway lead to the expression of adhesion molecules and increase the infiltration of eosinophils and mast cells, which ultimately leads to more severe clinical symptoms of the patient; cited process increases the production of cytokines, which causes differentiation of T cells to Th2 [20].

Prostaglandin D2 (PGD2) is an inflammatory lipid mediator produced by eosinophils. Signaling pathways which increase the tyrosine kinases PGD2 production and inhibition, in addition to reducing PGD2 production, reduces the eotaxin expression (one of the causative agents of eosinophil chemotaxis at the site of allergic inflammation [21]. Eosinophils stimulate inflammatory cells to produce IFN- γ ; eventually IFN- γ secretion leads to Transforming growth factor beta (TGF- β) production [22]. TGF- β is also produced by eosinophils.

Lung epithelial cells Fibrosis, leads to mucus secretion and obstruction of the pulmonary pathways, as well as increased cell proliferation. TGF- β increases the proliferation of lung cells and their fibrosis by activating the MAPK / P38 / ERK1 pathway [23, 24]. In addition to eosinophils, HLA polymorphisms may lead to IFN- γ production; polymorphism in the coding genes of HLA-DQB1 * 0302 and HLA-DRB1 is associated with activation of T cells and increased production of IFN- γ [25]. Although IFN- γ is said to be associated with TGF- β production and pulmonary cell fibrosis; like a double-edged sword, it has a preventive and therapeutic role in AERD.

HSP70 is one of the main protective factors against cell damage during inflammation; HSP70 expression is associated with increase in eosinophils and the allergic inflammation in the lung tissue. Therefore, BCL2-associated athanogene-1(BAG-1) causes eosinophil infiltration in the lung by binding to HSP70 and increasing its expression. Th2 cytokines such as IL-4 and IL-5 are some agents which increase the BAG-1 expression; IFN- γ is determined as the reduction factor for BAG-1 expression [26, 27].

Finally, it can be said that identifying eosinophils activating factors along with inhibiting eosinophils can be a good treatment strategy for ARED patients.

Innate lymphoid cells (ILC)

They are a rare type of immune cells, which are divided into three groups based on the transcription factors; ILC-2 is one of the cells, that increases during the allergic inflammation [28]. The number of these cells increases in AERD patients, which are not only involved in the pathogenesis of the disease; they play an essential role in disease progression and worsening the clinical condition of patients, by activating eosinophils and mast cells and even some inflammatory cells such as platelets [28, 29]. Lipid mediators derived from arachidonic acid metabolism are the activator and inhibitor factors for ILC-2 cells. LXA4 is one of the lipid mediators of arachidonic acid, which reduces ILC-2 activity [30]; it reduces LTC4 production and AERD progression, by inhibiting IFN- γ production of eosinophils [31].

GATA Binding Protein 3 (GATA3), is one of the effective transcription factor in Th2 differentiation, the expression

increases by binding to CRTH2 promoter region; there is also a binding site for the NFAT1 factor in the promoter area, which simultaneously connects the NFAT1 to GATA3 to express CRTH2 [32, 33]. ILC-2 activation is associated with cytokine secretion including IL-25, IL-5, IL-13 and Thymic stromal lymphopoietin-1 (TSLP-1). IL-25 and TSLP-1 are associated with mast cell and basophil activation and Th2 cytokine stimulation, which ultimately increase allergic reactions and AERD progression [34, 35].

Epithelial cells also play an important role in regulating ILC-2 function; glucagon-like peptide-1 (GLP-1) is expressed, at the surface of these cells. This receptor plays an important role in the insulin production. However, it has been shown to regulate ILC-2 function. GLP-1 reduces mucus secretion from lung cells by activating the cAMP / PKA pathway. In addition, it reduces the expression of CCL11 and CCL24; it also reduces the production of IL-13, IL-4 and IL-33 cytokines, which together reduce the function of ILC-2 and prevent the activation of eosinophils [36, 37].

In contrast, ILC-2 has been shown to play an important role in the regulation of neutrophil-mediated inflammation. It has been shown that ILC-2 increases the production of Arg-1 by activating STAT6, which ultimately leads to neutrophil chemotaxis and reduces inflammation. IL-13 and IL-33 produced by ILC-2 increase the STAT6 expression [38, 39].

Genetic variation

Although susceptibility to aspirin use is a major cause of AERD, recent studies have indicated that inherited or acquired genetic changes are major effective factor on AERD pathogenesis (Table 1). Polymorphisms in the coding genes of the immune system as well as inflammatory factors, increase AERD incidence and sensitivity of the patients to aspirin consumption [40]. Since few studies have been done about AERD-susceptible genes, AERD patients have been diagnosed based on the history of adverse reactions; due to anti-inflammatory drugs consumption, accurate identification of major altered genes in disease pathogenesis can be helpful as a diagnostic factor in disease detection [41]. Most of the genes polymorphisms of the involved enzymes in arachidonic acid metabolism have been identified [42, 43].

Arachidonate 15-lipoxygenase (ALOX15) belongs to the lipoxygenase family, which produces 15-hydroperoxy-eicosatetraenoic acid from arachidonic acid; it is expressed in various cells, including eosinophils, mast cells and epithelial lung cells. It also produces chemotactic substances from immune cells and induces inflammatory responses by stimulating immune system cells [44]. Recent results have found that -427G / A polymorphism in the ALOX15 enzyme gene increases the activity; it leads to eosinophil infiltration

Table 1 Some of genetic variations in the pathogenesis of AERD

Factor	Type of change	Location	Mechanism	References
GSDMB	SNP	17q21	Increase the proliferation of epithelial lung cells and apoptosis inhibition	[45]
FANCC	SNP	9q22.3	Induction inflammation through mobilization of hematopoietic progenitors	[51]
KIFC1	SNP	6p21.3	Up-regulation of the renin-angiotensin system	[52]
DCBLD2	SNP	3p12-q11	Increased proliferation of epithelial lung cells and inflammation Induction	[53, 54]
TRPM3	SNP	chromosome 9	Activation of mast cell and basophil through calcium channel	[55]
OBSCN	SNP	1q42.13	Dysregulation of Airway remodeling through intracellular calcium	[56]

GSDMB gasdermin B gene, *FANCC* Fanconi anemia, complementation group C, *SNP* single-nucleotide polymorphism, *KIFC1* kinesin family member C1, *DCBLD2* discoidin, CUB and LCCL domain-containing protein 2 *OBSCN* obscurin, cytoskeletal calmodulin and titin-interacting RhoGEF

into epithelial lung cells, therefore progresses AERD [42]. Some of the mutations that lead to eosinophils activation and leukotrienes production are listed in Table 2.

Solute carrier family 6 (neurotransmitter transporter, betaine / GABA) member 12 (SLC6A12) gene increases AERD susceptibility due to the polymorphism [45]. SLC6A12 is an ion transmitter on the surface of many cells, including airway epithelial cells. Activating the PI3K / AKT pathway increases IL-13 production, which ultimately increases mucus production in the airways of AERD patients by increasing SLC6A12 expression [46, 47]. It has been reported that IL-13 encoding gene polymorphism is associated with eosinophils increment and AERD progression. According to the role of IL-13 in SLC6A12 expression, polymorphism occurrence not only increase the amount of eosinophil, but also increases mucus production in the epithelial cells of the airways [41, 48].

Recently, Genome-wide association studies (GWASs) have been used in AERD patients to assess genetic changes and mutations. GWASs have also been used to assess the response to treatment of patients due to the genetic changes [49, 50]. Identifying the relationship between mutation and the patient response to treatment can play a prominent role in the design and implementation of the prevention and treatment strategies. In addition, this method can evaluate the genes, that make patients susceptible to AERD. For example, a study of a Korean population found that patients

with mutations in the gene encoding HLA-DPB1 were more likely to develop AERD [49].

Therapeutic strategies

Despite the variety of treatment strategies, the likelihood of recurrence of symptoms is high in patients with AERD; AERD treatment remains a major challenge in the current situation. The choice of treatment regimen in the AERD patients is generally based on the prevention of NSAIDs, aspirin desensitization following aspirin therapy or drug therapies. Avoiding NSAIDs due to the induction of COX-1 inhibiting mediators can prevent acute reactions, but chronic airway inflammation remains [61, 62].

On the other hand, one of the most common problems during the process of desensitization is severe asthma attacks, which must be controlled by leukotriene-modifying drugs (LMDs), as a pretreatment strategy [63]. Therefore, in addition to NSAIDs avoidance or desensitization, standard treatment strategies (to control prevalent asthma and rhino sinusitis in AERD) should also be in the list. The most important strategies for treating AERD are listed as following: drug therapies, aspirin desensitization, monoclonal antibodies (mAbs) and other therapies associated with AERD pathogenesis (Table 3) [64].

Table 2 Summary of polymorphisms involved in the eosinophil activation and leukotriene production

Gene	Polymorphism	Mechanism	References
P2Y12	742 T>C, 18 C>T	Activation eosinophils and platelets and cause leukotriene E4 production	[57]
IL-5	5993G4A, 5567C4G, 5091G4A	Activation eosinophils and mast cells and leukotriene over production	[58]
DCBLD2	T>C, G>C, G>A, A>G	Activation eosinophils and produce CysLTs from arachidonic acid	[54]
ALOX15	-427G/A, -272C/A, -217G/C	Eosinophils infiltration and leukotriene production	[42]
CCR3	-520 T/G and -174C/T	Cause eosinophilic infiltration into the asthmatic airway	[59]
CRTH2	-466 T>C, -129C>A	Cause eosinophilic infiltration into the asthmatic airway	[60]

DCBLD2 discoidin, CUB and LCCL domain-containing protein 2; *ALOX15*: arachidonate 15-lipoxygenase

Table 3 The most important mechanism and clinical outcome of AERD-related treatment strategies

Therapeutic strategies	Pharmacological drugs	Mechanism	Clinical outcome	References
<i>Intranasal corticosteroids</i>	Budesonide, Fluticasone, Mometasone, Triamcinolone	Phospholipase A2 inhibition	Reducing sinus inflammation, polyps formation and relapse	[4, 67, 68]
<i>Oral corticosteroid</i>	Prednisolone, Dexamethasone	Phospholipase A2 inhibition	Reducing nasal polyp tissue and mucosal edema	[65, 86]
<i>Inhaled corticosteroid</i>	Flovent HFA, Pulmicort Flex-haler	Phospholipase A2 inhibition	Minimizing the need for systemic corticosteroids and Reducing inflammatory activity	[64, 65]
<i>LMDs</i>	Montelukast, Zafirlukast, Pranlukast	CysLTR blocking	Improving pulmonary functions and reducing asthma symptoms	[69–71]
	Zileuton	5LO-inhibitors		
<i>Aspirin desensitization</i>	According to the desensitization protocol	Disruption of prostaglandins production	Reducing the prevalence of polyp function and episodes of sinusitis, as well as Minimizing the need for systemic corticosteroids	[64, 65, 87]
<i>Monoclonal antibodies</i>	Omalizumab	Anti-IgE mAb	Increasing the quality of life and improving lung function	[76–82, 88]
	Mepolizumab	anti-IL-5 mAb	Inhibiting eosinophilic hematopoiesis and increasing eosinophil apoptosis	
	Benralizumab	anti-IL-5 receptor mAb	Eosinophil/basophil destruction	
	Dupilumab	IL-4 α receptor antagonist	Inhibiting IL-3/IL-4 signaling and improving lung function	
<i>Anti-platelet therapies</i>	Prasugrel, Clopidogrel	P2Y12 receptor blocking	Suppression of pulmonary inflammation	[34, 82]
	Ifetroban	Thromboxane A2 receptor blocking	Inhibition of bronchoconstriction	
<i>CRTH2 antagonists</i>	ARRY-502, AZD1981	Prostaglandin-D2 blocking	Relieving airway inflammation	[2, 82, 89]

LMDs Leukotriene modifiers drugs, *CRTH2* Chemoattractant receptor-homologous molecule expressed on TH 2 cells, *CysLTR* cysteinyl leukotrienes receptor, *5LO-inhibitors* 5-lipoxygenase- inhibitors, *mAb* monoclonal antibody

Intranasal corticosteroids

Given that intranasal corticosteroids (such as budesonide, fluticasone, mometasone and triamcinolone) have high potency to reduce sinus inflammation, new polyps formation and rhinitis symptoms, they should be considered as the first-line therapy in AERD patients [65]. These medications prevent relapse and re-growth of polyps after surgery by A2 Phospholipase (in the arachidonic acid pathway) inhibition [66]. For any patients with asthma, who develop the least airway symptoms, corticosteroids should be given with or without long-term controllers [67]. However, a subset of patients with AERD requires permanent systemic corticosteroids. In one study about 32% of AERD patients, who use daily systemic corticosteroids were identified [68]; although corticosteroids have many benefits, the continuous use does not cause good results and increases destructive effects.

Oral and inhaled corticosteroids

If clinical symptoms persist in patients, despite different treatment strategies, oral corticosteroids (such as prednisolone and dexamethasone) may be useful in treating and management of AERD patients. The action mechanism of oral corticosteroids is similar to the intranasal ones (inhibition of phospholipase A2), and significantly reduces nasal polyp tissue and mucosal edema [65]. Although the response to oral corticosteroids is very diverse in AERD, but most effects occur within 2–3 weeks of treatment onset [57]. According to the harmful side effects, physicians should be cautious to prescribe oral corticosteroids; they should not be considered as the first-line therapy [65]. On the other hand, asthma management in AERD is based on the recent guidelines by inhaled corticosteroids (such as flovent HFA and Pulmicort Flexhaler), in association with bronchodilators therapy and B2-agonists; the main reason to use inhaled corticosteroids

is to reduce inflammatory activity and minimize the need for systemic prescription [64].

Leukotriene modifier drugs

Given that overproduction of CysTLs is a critical feature in the pathogenesis of AERD, various studies have declared that leukotriene modifier drugs (LMDs) can be a suitable strategy [61]. LMDs minimize the specific inflammatory reactions of patients, who had been exposed to NSAIDs, via blocking cysteinyl leukotriene receptor (CysLTR) by leukotriene receptor antagonists (such as montelukast, zafirlukast, pranlukast); they can act by inhibiting 5-lipoxygenase by 5LO-inhibitors (such as zileuton), too [69]. Leukotriene receptor antagonists, especially montelukast and zileuton, both improve pulmonary function, reduce asthma symptoms and increase the quality of life in AERD patients.

Montelukast is more common than 5LO-inhibitors, due to its lower cost and side effects [70]. Also, zileuton increases the risk of hepatotoxicity, so patients' need for serial monitoring of hepatic enzymes increases, which is not economically viable [71].

Aspirin desensitization

This is the gold standard strategy for AERD patients. Therapeutic purposes in aspirin desensitization include reducing the prevalence of polyp function, episodes of sinusitis and reducing the need for systemic corticosteroids [72]. Aspirin desensitization increases resistance to aspirin and other NSAIDs [61]. LMDs can reduce the safety of oral aspirin challenge, that occurs following aspirin desensitization by decreasing the severity of asthma responses. For this reason, LMDs administration is recommended as a pretreatment, at least one week before oral aspirin therapy [65].

Failure to use LMDs may reduce the risk of forced expiratory volume in 1-s (FEV1) to less than 80% of the predicted amount, as well as respiratory capacity depletion [73]. Another measure to control the effects of aspirin desensitization is the availability of an intensive care unit (ICU). One of the most significant problems during the desensitization process is severe asthma attacks. Although researches have reported a small number of patients who need ICUs during the desensitization process; it is strongly recommended to control the asthma episodes during desensitization [64, 74].

Monoclonal antibodies (mAbs)

So far, no specific researches has been done on the use of mAbs to treat AERD patients in particular; however, the results of mAbs consumption in patients with asthma and allergy have opened a new window for the effectiveness of these medications in AERD. One of the most important

mAbs is Omalizumab (anti-IgE mAb), which therapeutic properties have been proven in patients with asthma [67]. Omalizumab is a recombinant human antibody that inhibits IgE binding to the high-affinity IgE receptor (FcεR) [75]. Some studies have indicated to Omalizumab role in improving clinical symptoms, quality of life and lung function of AERD patients [62, 76]. According to the AERD pathogenesis, which is not Ig-E dependent, the benefits of this mAb remain a challenge for the treatment of patients with AERD [77]. However, more researches are needed on the use of Omalizumab, due to its mechanism and functions.

Regarding to the undeniable role of cytokines in the pathogenesis and exacerbation of symptoms, researches on anti-IL-5 mAb (such as Mepolizumab, Reslizumab, and Benralizumab) as well as anti-IL-4 receptor antagonists (such as Dupilumab) is suitable for treatment design of AERD, as well as control severe asthma [78, 79].

Mepolizumab is an anti-IL-5 mAb, that inhibits eosinophilic hematopoiesis and increases eosinophil apoptosis [80]; it can be useful in eosinophilic asthma and minimizing nasal polyps [78]. Benralizumab is an anti-IL-5 receptor mAb, which leads to eosinophil/basophil destruction by antibody-dependent cell-mediated cytotoxicity, unlike anti-IL-5 mAbs [81]; it can be used to treat patients with eosinophilic asthma, but its therapeutic properties have not been established in AERD patients [81].

Dupilumab is an IL-4 α antagonist receptor, which inhibits IL-4 / IL-13 signaling. Clinical researches have shown that the use of Dupilumab in eosinophilic asthma individuals has been associated with nasal symptoms reduction and improved lung function [79]; it can decrease the level of TH2-associated inflammatory markers [82]. However, so far, no specific studies have examined the effects of this mAb on AERD patients. It should be noted that Omalizumab and Mepolizumab are FDA approved, unlike Dupilumab; they are more economical too [82, 83].

Anti-platelet therapies

Today, clinical trials with platelet-targeted therapies offer promising prospects for advancing AERD therapy. Platelets stimulate leukocyte aggregation to produce excessive leukotrienes in AERD; P2Y12 receptor antagonists, including clopidogrel and Prasugrel can suppress pulmonary inflammation by reducing leukocyte aggregation [84]. On the other hand, the thromboxane receptor can be another platelet related therapeutic goal, due to its role in strengthening bronchospasm; therefore, researches on thromboxane receptor antagonists such as Ifetroban are performed in patients with AERD; they act by blocking the bronchoconstriction signals [82, 84].

CRTH2 antagonists

Due to the overexpression of prostaglandin-D2 and inflammatory lipid mediators in AERD, several studies have focused on CRTH2 antagonists such as ARRY-502 and AZD1981, recently [2].

Prostaglandin-D2 leads to the recall of allergic effector cells, such as eosinophils, basophils and ILC-2 s to respiratory tissue, through CRTH2 signaling. Therefore, CRTH2 antagonists appear to be effective on relieving airway inflammation in the allergic reactions or even in AERD [2, 85].

Conclusion

As a general conclusion and a possible idea for designing a treatment strategy for ARED patients, it can be said that NSAIDs act as a double edge sword; They and, on the other hand, they can change them worse. Sex hormones can prevent disease progression through the molecular mechanisms involved in leukotrienes. Identifying the molecular pathways that occur between sex hormones and leukotrienes could be a good idea for future researches, to treat ARED patients.

Acknowledgements We wish to thank all our colleagues in Vali-e-Asr Hospital and Allied Health Sciences School, Zanjan University of Medical Sciences.

Authors contributions MN has conceived the manuscript and revised it. HH and NS wrote the manuscript. MM and AB design the tables. M,M conducted revised.

Funding Not applicable.

Data availability The datasets used analyzed during the current study are available from the corresponding author on reasonable request.

Declaration

Conflict of interest The authors declared that they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable.

References

- Renjiao L, Fengming L (2020) The safety and efficacy of aspirin desensitization combined with long-term aspirin therapy in Aspirin-exacerbated respiratory disease. *J Investigational AllergolClinImmunol* 30(5):327–333
- Taniguchi M, Mitsui C, Hayashi H, Ono E, Kajiwara K, Mita H et al (2019) Aspirin-exacerbated respiratory disease (AERD): current understanding of AERD. *Allergol Inter* 68(3):289–295
- Kowalski ML, Makowska J, Blanca M, Bavek S, Bochenek G, Bousquet J et al (2011) Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs)—classification, diagnosis and management: review of the EAACI/ENDA# and GA2LEN/HANNA. *Allergy* 66(7):818–829
- Stevenson DD, Szczeklik A (2006) Clinical and pathologic perspectives on aspirin sensitivity and asthma. *J Allergy ClinImmunol* 118(4):773–786
- Pleskow WW, Stevenson DD, Mathison DA, Simon RA, Schatz M, Zeiger RS (1982) Aspirin desensitization in aspirin-sensitive asthmatic patients: clinical manifestations and characterization of the refractory period. *J Allergy ClinImmunol* 69(1):11–19
- Laidlaw TM (2018) Pathogenesis of NSAID-induced reactions in aspirin-exacerbated respiratory disease. *World J Otorhinolaryngol-Head Neck Surg* 4(3):162–168
- Aksu K, Kurt E, Alatas Ö, Gülbas Z, editors. Effect of aspirin desensitization on T-cell cytokines and plasma lipoxins in aspirin-exacerbated respiratory disease. *Allergy & Asthma Proceedings*; 2014.
- Seyedian SS, Nokhostin F, Malamir MD (2019) A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. *Journal of medicine and life* 12(2):113
- Lassila R, Editor (2016) Platelet function tests in bleeding disorders. *Seminars in thrombosis and hemostasis*. Thieme Medical Publishers, NY
- Liu T, Barrett NA, Kanaoka Y, Buchheit K, Laidlaw TM, Garofalo D et al (2019) Cysteinyl leukotriene receptor 2 drives lung immunopathology through a platelet and high mobility box 1-dependent mechanism. *Mucosal Immunol* 12(3):679–690
- Maugeri N, Evangelista V, Celardo A, Dell’Elba G, Martelli N, Piccardoni P et al (1994) Polymorphonuclear leukocyte-platelet interaction: role of P-selectin in thromboxane B2 and leukotriene C4 cooperative synthesis. *ThrombHaemost* 72(09):450–456
- Liu T, Laidlaw TM, Katz HR, Boyce JA (2013) Prostaglandin E2 deficiency causes a phenotype of aspirin sensitivity that depends on platelets and cysteinylleukotrienes. *ProcNatlAcadSci* 110(42):16987–16992
- Rashidi H, Shahbazian H, Nokhostin F, Bahadoram M, Payami SP (2015) The association between concentration of Uric Acid and metabolic syndrome among adolescents. *Tehran University Medical Journal TUMS Publications* 73(8):600–607
- Laidlaw TM, Cahill KN, Cardet JC, Murphy K, Cui J, Dioneda B et al (2019) A trial of type 12 purinergic (P2Y12) receptor inhibition with prasugrel identifies a potentially distinct endotype of patients with aspirin-exacerbated respiratory disease. *J Allergy ClinImmunol*. 143(1):316–324
- Tunjungputri RN, van der Ven AJ, Riksen N, Rongen G, Tacke S, van den Berg T et al (2015) Differential effects of platelets and platelet inhibition by ticagrelor on TLR2-and TLR4-mediated inflammatory responses. *ThrombHaemost* 113(05):1035–1045
- Dinkla S, van Cranenbroek B, van der Heijden WA, He X, Wallbrecher R, Dumitriu IE et al (2016) Platelet microparticles inhibit IL-17 production by regulatory T cells through P-selectin. *Blood* 127(16):1976–1986
- Bandeira-Melo C, Bozza PT, Weller PF (2002) The cellular biology of eosinophil eicosanoid formation and function. *J Allergy ClinImmunol* 109(3):393–400
- Rajaei E, Jalali MT, Pezeshki SMS, Rezaeeyan H, Maniati M, Elyasi M et al (2020) Dose HLA-B*5, 7, 8, 27, and 51 Antigens Associated to Behcet’s disease? A Study in Southwestern Iran. *Curr Rheumatology Rev* 16(2):120–124
- Choi M-R, Xu J, Lee S, Yeon S-H, Park S-K, Rha K-S et al (2020) Chloroquine treatment suppresses mucosal inflammation

- in a mouse model of eosinophilic chronic rhinosinusitis. *Allergy Asthma Immunol Res* 12(6):994
20. Wong C, Wang C, Ip W, Tian Y, Lam C (2005) Role of p38 MAPK and NF- κ B for chemokine release in coculture of human eosinophils and bronchial epithelial cells. *ClinExpImmunol* 139(1):90–100
 21. El-Shazly A, Roncarati P, Lejeune M, Lefebvre P, Delvenne P (2017) Tyrosine kinase inhibition is an important factor for gene expression of CRTH2 in human eosinophils and lymphocytes: A novel mechanism for explaining eosinophils recruitment by the neuro-immune axis in allergic rhinitis. *IntImmunopharmacol* 45:180–186
 22. Steinke JW, Negri J, Liu L, Payne SC, Borish L (2014) Aspirin activation of eosinophils and mast cells: implications in the pathogenesis of aspirin-exacerbated respiratory disease. *J Immunol* 193(1):41–47
 23. Minshall EM, Leung DY, Martin RJ, Song YL, Cameron L, Ernst P et al (1997) Eosinophil-associated TGF- β 1 mRNA expression and airways fibrosis in bronchial asthma. *Am J Respir Cell Mol Biol* 17(3):326–333
 24. Wang D, Yan Z, Bu L, An C, Deng B, Zhang J et al (2019) Protective effect of peptide DR8 on bleomycin-induced pulmonary fibrosis by regulating the TGF- β /MAPK signaling pathway and oxidative stress. *ToxicolApplPharmacol* 382:114703
 25. Esmailzadeh H, Nabavi M, Amirzargar AA, Aryan Z, Arshi S, Bemanian MH et al (2015) HLA-DRB and HLA-DQ genetic variability in patients with aspirin-exacerbated respiratory disease. *Am J Rhinol Allergy* 29(3):e63–e69
 26. Lin D, Lin H, Xiong X (2014) Expression and role of BAG-1 in eosinophilic and non-eosinophilic chronic rhinosinusitis with nasal polyps. *Inflammation* 37(6):1912–1918
 27. Kikuchi K, Abe S, Kodaira K, Yukawa T, Hozawa S, Mochizuki H et al (2013) Heat shock protein 70 gene polymorphisms in Japanese patients with aspirin-exacerbated respiratory disease. *J Investig Med* 61(4):708–714
 28. Doherty TA, Broide DH (2018) Lipid regulation of group 2 innate lymphoid cell function: moving beyond epithelial cytokines. *J Allergy ClinImmunol* 141(5):1587–1589
 29. Doherty TA (2015) At the bench: understanding group 2 innate lymphoid cells in disease. *J LeukocBiol* 97(3):455–467
 30. von Moltke J, O'Leary CE, Barrett NA, Kanaoka Y, Austen KF, Locksley RM (2017) Leukotrienes provide an NFAT-dependent signal that synergizes with IL-33 to activate ILC2s. *J Exp Med* 214(1):27–37
 31. Rozsasi A, Heinemann A, Keck T (2016) Release of cyclooxygenase-2 and lipoxin A4 from blood leukocytes in aspirin-exacerbated respiratory disease. *Allergy Rhinology* 7(3):0172
 32. MacLean Scott E, Solomon LA, Davidson C, Storie J, Palikhe NS, Cameron L (2018) Activation of Th2 cells downregulates CRTh2 through an NFAT1 mediated mechanism. *PLoS ONE* 13(7):e0199156
 33. Bachert C, Zhang L, Gevaert P (2015) Current and future treatment options for adult chronic rhinosinusitis: focus on nasal polypsis. *J Allergy ClinImmunol* 136(6):1431–1440
 34. Buchheit KM, Cahill KN, Katz HR, Murphy KC, Feng C, Lee-Sarwar K et al (2016) Thymic stromal lymphopoietin controls prostaglandin D2 generation in patients with aspirin-exacerbated respiratory disease. *J Allergy ClinImmunol* 137(5):1566–1576
 35. Mitchell PD, O'Byrne PM (2017) Biologics and the lung: TSLP and other epithelial cell-derived cytokines in asthma. *PharmacolTher* 169:104–112
 36. Toki S, Goleniewska K, Reiss S, Zhang J, Bloodworth MH, Stier MT et al (2018) Glucagon-like peptide 1 signaling inhibits allergen-induced lung IL-33 release and reduces group 2 innate lymphoid cell cytokine production in vivo. *J Allergy ClinImmunol* 142(5):1515–1528
 37. Cho YJ, Kim S, Orimo K, Saito H, Matsumoto K, Morita H et al (2020) Does the Difference in Microbial Patterns in the Airways Induce Distinct Endotypes of Asthma? *Allergy, asthma & immunology research* 12(3):375–377
 38. Liang Y, Yi P, Yuan DMK, Jie Z, Kwota Z, Soong L et al (2019) IL-33 induces immunosuppressive neutrophils via a type 2 innate lymphoid cell/IL-13/STAT6 axis and protects the liver against injury in LCMV infection-induced viral hepatitis. *Cell MolImmunol* 16(2):126–137
 39. Kim H, Yu S, Choi H, Effects of particulate air pollution on tuberculosis development in seven major cities of Korea from, (2010) to 2016: methodological considerations involving long-term exposure and time lag. *Epidemiology and health* 2020:42
 40. Chang H, Shin S, Lee T, Bae D, Park J, Kim Y et al (2015) Development of a genetic marker set to diagnose aspirin-exacerbated respiratory disease in a genome-wide association study. *Pharmacogenomics J* 15(4):316–321
 41. Kurosawa M, Yukawa T, Hozawa S, Mochizuki H (2015) Recent advance in investigation of gene polymorphisms in Japanese patients with aspirin-exacerbated respiratory disease. *AllergolImmunopathol* 43(1):92–100
 42. Song Y-S, Yang E-M, Kim S-H, Jin HJ, Park H-S (2012) Effect of genetic polymorphism of ALOX15 on aspirin-exacerbated respiratory disease. *Int Arch Allergy Immunol* 159(2):157–161
 43. Losol P, Kim S-H, Shin YS, Ye YM, Park H-S (2013) A genetic effect of IL-5 receptor α polymorphism in patients with aspirin-exacerbated respiratory disease. *Experimental Mol Med* 45(3):e14
 44. Claesson H-E (2009) On the biosynthesis and biological role of eoxins and 15-lipoxygenase-1 in airway inflammation and Hodgkin lymphoma. *Prostaglandins Other Lipid Mediat* 89(3–4):120–125
 45. Pasaje CFA, Kim JH, Park BL, Cheong HS, Chun JY, Park TJ et al (2010) Association of SLC6A12 variants with aspirin-intolerant asthma in a Korean population. *Ann Hum Genet* 74(4):326–334
 46. Corry DB, Kheradmand F (2007) A new link to airway obstruction in asthma. *Nat Med* 13(7):777–778
 47. Lu WY, Inman M (2009) γ -aminobutyric acid nurtures allergic asthma. *ClinExp Allergy* 39(7):956–961
 48. Haybar H, Shahrabi S, Rezaeeyan H, Jodat H, Saki N (2019) Strategies to inhibit arsenic trioxide-induced cardiotoxicity in acute promyelocytic leukemia. *J Cell Physiol* 234(9):14500–14506
 49. Park BL, Kim T-H, Kim J-H, Bae JS, Pasaje CFA, Cheong HS et al (2013) Genome-wide association study of aspirin-exacerbated respiratory disease in a Korean population. *Hum Genet* 132(3):313–321
 50. Shin S-W, Park J, Kim Y-J, Uh S-t, Choi BW, Kim M-k et al (2012) A highly sensitive and specific genetic marker to diagnose aspirin-exacerbated respiratory disease using a genome-wide association study. *DNA Cell Biol* 31(11):1604–1609
 51. Kim J-H, Park B-L, Pasaje CFA, Bae JS, Park JS, Park SW et al (2012) Association of FANCC polymorphisms with FEV1 decline in aspirin exacerbated respiratory disease. *MolBiol Rep* 39(3):2385–2394
 52. Pasaje CFA, Bae JS, Park B-L, Kim J-H, Cheong HS, Uh S-T et al (2012) Genetic variations in KIFC1 and the risk of aspirin exacerbated respiratory disease in a Korean population: an association analysis. *MolBiol Rep* 39(5):5913–5919
 53. Kobuke K, Furukawa Y, Sugai M, Tanigaki K, Ohashi N, Matsumori A et al (2001) ESDN, a novel neuropilin-like membrane protein cloned from vascular cells with the longest secretory signal sequence among eukaryotes, is up-regulated after vascular injury. *J BiolChem* 276(36):34105–34114
 54. Park T-J, Kim J-H, Park B-L, Cheong HS, Bae JS, Pasaje CF et al (2012) Potential association of DCBLD2 polymorphisms with fall rates of FEV1 by aspirin provocation in Korean asthmatics. *J Korean Med Sci* 27(4):343

55. Narayanankutty A, Palma-Lara I, Pavón-Romero G, Pérez-Rubio G, Camarena Á, Terán LM et al (2016) Association of TRPM3 polymorphism (rs10780946) and aspirin-exacerbated respiratory disease (AERD). *Lung* 194(2):273–279
56. Kim J-H, Park B-L, Pasaje CFA, Kim Y, Bae JS, Park JS et al (2012) Contribution of the OBSCN nonsynonymous variants to aspirin exacerbated respiratory disease susceptibility in Korean population. *DNA Cell Biol* 31(6):1001–1009
57. Losol P, Palikhe NS, Lee JW, Palikhe S, Kim M-A, Yang E-M et al (2015) Association of P2RY12 polymorphisms with eosinophil and platelet activation in patients with aspirin-exacerbated respiratory disease. *Annals Allergy Asthma Immunol* 114(5):423–424
58. Losol P, Shin YS (2013) A genetic effect of IL-5 receptor a polymorphism in patients with aspirin-exacerbated respiratory disease. *ExpMol Med* 45(3):1–7
59. Kim S-H, Yang E-M, Lee H-N, Choi G-S, Ye Y-M, Park H-S (2010) Association of the CCR3 gene polymorphism with aspirin exacerbated respiratory disease. *Respir Med* 104(5):626–632
60. Palikhe N, Kim SH, Cho BY, Ye YM, Choi GS, Park HS (2010) Genetic variability in CRTH2 polymorphism increases eotaxin-2 levels in patients with aspirin exacerbated respiratory disease. *Allergy* 65(3):338–346
61. Cook KA, Stevenson DD (2016) Current complications and treatment of aspirin-exacerbated respiratory disease. *Expert Rev Respiratory Med* 10(12):1305–1316
62. Yeung WYW, Park HS (2020) Update on the management of non-steroidal anti-inflammatory drug hypersensitivity. *Yonsei Med J* 61(1):4
63. Education NA, Program P (2007) Expert panel report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy ClinImmunol* 120(5 Suppl):S94–S138
64. Rodríguez-Jiménez JC, Moreno-Paz FJ, Terán LM, Guaní-Guerra E (2018) Aspirin exacerbated respiratory disease: current topics and trends. *Respir Med* 135:62–75
65. Simon RA, Dazy KM, Waldram JD (2015) Aspirin-exacerbated respiratory disease: characteristics and management strategies. *Expert Rev ClinImmunol* 11(7):805–817
66. Choi J-H, Kim J-H, Park H-S (2015) Upper airways in aspirin-exacerbated respiratory disease. *CurrOpin Allergy ClinImmunol* 15(1):21–26
67. Kennedy JL, Stoner AN, Borish L (2016) Aspirin-exacerbated respiratory disease: Prevalence, diagnosis, treatment, and considerations for the future. *Am J RhinolAller* 30(6):407–413
68. Berges-Gimeno MP, Simon RA, Stevenson DD (2002) The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 89(5):474–478
69. Berges-Gimeno M, Simon R, Stevenson D (2002) The effect of leukotriene-modifier drugs on aspirin-induced asthma and rhinitis reactions. *ClinExp Allergy* 32(10):1491–1496
70. Steinke JW, Wilson JM (2016) Aspirin-exacerbated respiratory disease: pathophysiological insights and clinical advances. *Journal of asthma and allergy* 9:37
71. Dahlén S-E, Malmstrom K, Nizankowska E, Dahlén B, Kuna P, Kowalski M et al (2002) Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. *Am J RespirCrit Care Med* 165(1):9–14
72. Berges-Gimeno MP, Simon RA, Stevenson DD (2003) Early effects of aspirin desensitization treatment in asthmatic patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 90(3):338–341
73. Spies JW, Valera FCP, Cordeiro DL, Mendonça TNd, Leite MGJ, Tamashiro E et al (2016) The role of aspirin desensitization in patients with aspirin-exacerbated respiratory disease (AERD). *Brazilian J Otorhinolaryngol* 82(3):263–268
74. Woo S-D, Luu QQ, Park H-S (2020) NSAID-exacerbated respiratory disease (NERD): from pathogenesis to improved care. *Frontiers in Pharmacology* 11:1147
75. Bobolea I, Barranco P, Fiandor A, Cabañas R, Quirce S (2010) Omalizumab: a potential new therapeutic approach for aspirin-exacerbated respiratory disease. *J InvestAllergolClinImmunol* 20(5):448–449
76. Hayashi H, Mitsui C, Nakatani E, Fukutomi Y, Kajiwaru K, Watai K et al (2016) Omalizumab reduces cysteinyl leukotriene and 9 [alpha], 11 [beta]-prostaglandin F2overproduction in aspirin-exacerbated respiratory disease. *J Allergy ClinImmunol* 137(5):1585
77. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruycck N, Bauters W et al (2013) Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy ClinImmunol* 131(1):110–116
78. Gevaert P, Van Bruaene N, Cattaert T, Van Steen K, Van Zele T, Acke F et al (2011) Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy ClinImmunol* 128(5):989–995
79. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F et al (2013) Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 368(26):2455–2466
80. Mahdavinia M, Batra PS, Codispoti C (2019) Mepolizumab utility in successful aspirin desensitization in aspirin-exacerbated respiratory disease in a refractory case. *Ann Allergy Asthma Immunol* 123(3):311–312
81. Varricchi G, Bagnasco D, Borriello F, Heffler E, Canonica GW (2016) Interleukin-5 pathway inhibition in the treatment of eosinophilic respiratory disorders: evidence and unmet needs. *CurrOpin Allergy ClinImmunol* 16(2):186
82. Buchheit KM, Laidlaw TM (2016) Update on the management of aspirin-exacerbated respiratory disease. *Allergy, asthma & immunology research* 8(4):298
83. Thaçi D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K et al (2016) Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *The Lancet* 387(10013):40–52
84. Laidlaw TM, Boyce JA (2015) Platelets in patients with aspirin-exacerbated respiratory disease. *Journal of Allergy and Clinical Immunology* 135(6):1407–1414
85. Uller L, Mathiesen JM, Alenmyr L, Korsgren M, Ulven T, Högborg T et al (2007) Antagonism of the prostaglandin D 2 receptor CRTH2 attenuates asthma pathology in mouse eosinophilic airway inflammation. *Respir Res* 8(1):1–10
86. Walgama ES, Hwang PH (2017) Aspirin-exacerbated respiratory disease. *OtolaryngolClin North Am* 50(1):83–94
87. Spies JW, Valera FCP, Cordeiro DL, de Mendonça TN, Leite MGJ, Tamashiro E et al (2016) The role of aspirin desensitization in patients with aspirin-exacerbated respiratory disease (AERD). *Brazilian journal of otorhinolaryngology* 82(3):263–268
88. Maleknia M, Valizadeh A, Pezeshki S, Saki N. Immunomodulation in leukemia: cellular aspects of anti-leukemic properties. *Clinical and Translational Oncology*. 2019:1–10.
89. Uller L, Mathiesen JM, Alenmyr L, Korsgren M, Ulven T, Högborg T et al (2007) Antagonism of the prostaglandin D 2 receptor CRTH2 attenuates asthma pathology in mouse eosinophilic airway inflammation. *Respir Res* 8(1):16

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.