Received: 23 November 2021 | Revised: 25 January 2022 | Accepted: 11 February 2022

DOI: 10.1111/all.15258

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

POSITION PAPER

Effects of non-steroidal anti-inflammatory drugs and other eicosanoid pathway modifiers on antiviral and allergic responses: EAACI task force on eicosanoids consensus report in times of COVID-19

Milena Sokolowska[1,2] | G Enrico Rovati[3] | Zuzana Diamant[4,5,6] | Eva Untersmayr[7] | Jürgen Schwarze[8] | Zuzanna Lukasik[1,9] | Florentina Sava[10] | Alba Angelina[11] | Oscar Palomares[11] | Cezmi Akdis[1,2] | Liam O'Mahony[12] | Milos Jesenak[13] | Oliver Pfaar[14] | María José Torres[15] | Marek Sanak[16] | Sven-Erik Dahlén[17] | Grzegorz Woszczek[18]

[1]Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland

[2]Christine Kühne - Center for Allergy Research and Education (CK-CARE), Davos, Switzerland

[3]Department of Pharmaceutical Sciences, Section of Pharmacology and Biosciences, University of Milan, Milano, Italy

[4]Department of Respiratory Medicine and Allergology, Skane University Hospital, Lund, Sweden

[5]Department Microbiology Immunology and Transplantation, Ku Leuven, Catholic University of Leuven, Belgium

[6]Department of Respiratory Medicine, First Faculty of Medicine, Charles University and Thomayer Hospital, Prague, Czech Republic

[7]Institute of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria

[8]Child Life and Health and Centre for Inflammation Research, The University of Edinburgh, Edinburgh, UK

[9]VIB Center for Inflammation Research, Ghent University, Ghent, Belgium

[10]London North Genomic Laboratory Hub, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK

[11]Department of Biochemistry and Molecular Biology, School of Chemistry, Complutense University, Madrid, Spain

[12]Departments of Medicine and Microbiology, APC Microbiome Ireland, University College Cork, Cork, Ireland

[13]Department of Pulmonology and Phthisiology, Department of Allergology and Clinical Immunology, Department of Pediatrics, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, University Teaching Hospital in Martin, Slovakia

[14]Department of Otorhinolaryngology, Head and Neck Surgery, Section of Rhinology and Allergy, University Hospital Marburg, Philipps-Universität Marburg, Marburg, Germany

[15]Allergy Unit, Málaga Regional University Hospital-IBIMA-UMA, Málaga, Spain

[16]Department of Medicine, Jagiellonian University Medical College, Krakow, Poland

[17]Institute of Environmental Medicine and the Centre for Allergy Research, Karolinska Institute, and the Department of Respiratory Medicine, Karolinska University Hospital, Stockholm, Sweden

[18]Asthma UK Centre in Allergic Mechanisms of Asthma, School of Immunology and Microbial Sciences, King's College London, London, UK

Correspondence
Milena Sokolowska, Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Herman-Burchard-Strasse 9, CH-7265 Davos-Wolfgang.
Email: milena.sokolowska@siaf.uzh.ch

Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) and other eicosanoid pathway modifiers are among the most ubiquitously used medications in the general population. Their broad anti-inflammatory, antipyretic, and analgesic effects are applied against symptoms of respiratory infections, including SARS-CoV-2, as well as in other acute and chronic

Grzegorz Woszczek, Asthma UK Centre in Allergic Mechanisms of Asthma, School of Immunology and Microbial Sciences, King's College London, 5th Floor, Tower Wing, Guy's Hospital, London SE1 9RT, UK.
Email: grzegorz.woszczek@kcl.ac.uk

Funding information
EAACI TF on Eicosanoids received funding from the EAACI.

inflammatory diseases that often coexist with allergy and asthma. However, the current pandemic of COVID-19 also revealed the gaps in our understanding of their mechanism of action, selectivity, and interactions not only during viral infections and inflammation, but also in asthma exacerbations, uncontrolled allergic inflammation, and NSAIDs-exacerbated respiratory disease (NERD). In this context, the consensus report summarizes currently available knowledge, novel discoveries, and controversies regarding the use of NSAIDs in COVID-19, and the role of NSAIDs in asthma and viral asthma exacerbations. We also describe here novel mechanisms of action of leukotriene receptor antagonists (LTRAs), outline how to predict responses to LTRA therapy and discuss a potential role of LTRA therapy in COVID-19 treatment. Moreover, we discuss interactions of novel T2 biologicals and other eicosanoid pathway modifiers on the horizon, such as prostaglandin D2 antagonists and cannabinoids, with eicosanoid pathways, in context of viral infections and exacerbations of asthma and allergic diseases. Finally, we identify and summarize the major knowledge gaps and unmet needs in current eicosanoid research.

KEYWORDS
asthma, biologicals, COVID-19, LTRA, NSAID

1 | INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) and other eicosanoid pathway modifiers are one of the most frequently used anti-inflammatory medications worldwide against symptoms of infections, other acute and chronic inflammatory diseases, and pain. Eicosanoids, including prostaglandins (PGs), leukotrienes (LTs), thromboxanes (TXs), hydroxyeicosatetraenoic acids (HETEs), lipoxins (LXs), and many recently proposed pro-resolving mediators constitute a wide range of active lipid mediators possessing pro- and anti-inflammatory, as well as pro-resolution properties.[1] They are products of the major unsaturated fatty acids: arachidonic acid (AA), dihomo-γ-linolenic acid (DHGLA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), metabolized in three main pathways: cyclooxygenase (COX), lipoxygenase (LO or LOX), and cytochrome P450 (Figure 1). Those active lipid mediators play substantial roles in the development and resolution of inflammation, including allergic and viral inflammation, which we have reviewed extensively in the previous report.[1] Even though NSAIDs and other eicosanoid pathway modifiers are so commonly consumed and are relatively safe for the majority of people, the current pandemic of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) revealed substantial knowledge gaps in understanding their modes of action, benefits, and risks related to their use in patients with respiratory and allergic diseases. Unfortunately, this resulted in the conflicting messages sent to the public from the scientific community. Therefore, we, the European Academy of Allergy and Clinical Immunology Task Force (EAACI TF) on Eicosanoids, here critically review the most recent findings on the roles of NSAIDs, leukotriene antagonists (LTRAs), prostaglandin D_2 (PGD_2) receptor antagonists, and cannabinoids, as well as we summarize their selectivity, and additional modes of actions in allergic airway diseases, drug allergy, and respiratory virus infections. In addition, we also describe here the effects of novel T2 biologicals used in allergic diseases on eicosanoid pathways.

2 | NSAIDS IN ASTHMA AND VIRAL ASTHMA EXACERBATIONS

Aside from NSAIDs-exacerbated respiratory disease (NERD), NSAIDs are usually well tolerated by patients with asthma, and therefore, they are often used in real life against symptoms of respiratory infection such as fever and pain, even during asthma exacerbations together with intensified asthma treatment in children and adults.[2] Current Global Initiative for Asthma (GINA) guidelines are stating with evidence level A, that aspirin and other NSAIDs are generally not contraindicated in patients with asthma, unless there is a history of previous reactions to those medications. Nevertheless, it is still not very well studied whether NSAIDs facilitate or inhibit achievement of asthma control following exacerbations, and if they affect the speed of resolution of airway inflammation. Exacerbations of asthma are most often induced by common respiratory viruses including rhinovirus (RV), respiratory syncytial virus (RSV), bocavirus, influenza viruses, adenovirus, and others.[3-5] RV is responsible for up to 76% of exacerbations of wheeze in children and up to 83% of asthma attacks in adults.[3-5] Recurrent viral infections do not only cause acute disease and exacerbations of established disease, but they also contribute to the pathophysiology of early wheezing in children and the development of asthma. Prophylaxis of RSV-induced bronchiolitis with palivizumab, an anti-RSV monoclonal antibody, in late preterm infants decreased the risk of recurrent infant wheeze and

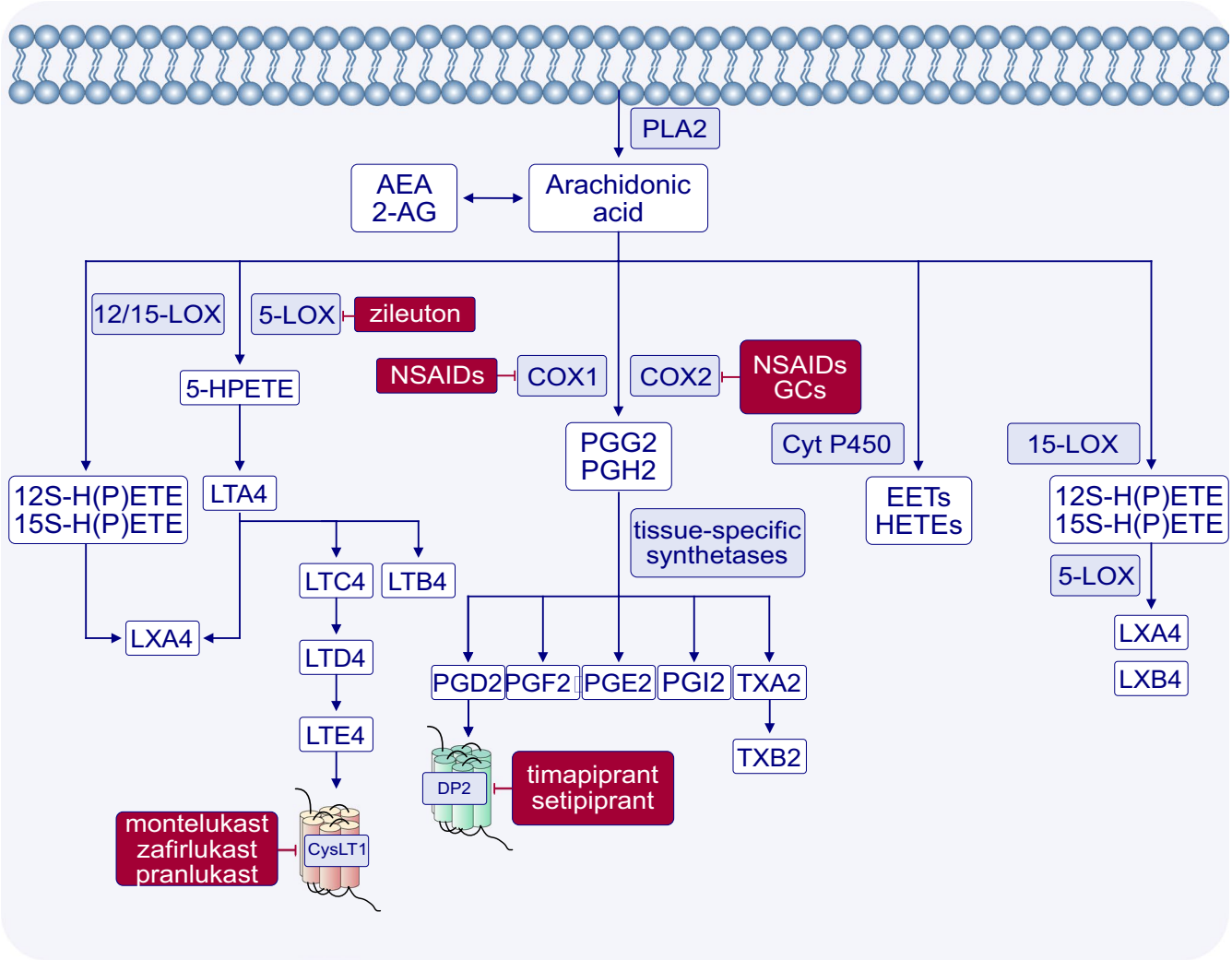

FIGURE 1 Eicosanoid biosynthesis and signaling pathways are therapeutic targets of medications used in the treatment of infections, acute and chronic inflammatory diseases (including asthma and allergy) and pain. Glucocorticosteroids (GCs), non-steroidal anti-inflammatory drugs (NSAIDs), leukotriene receptor antagonists (LTRAs, e.g., montelukast, zafirlukast, pranlukast), 5-lipoxygenase (5-LOX) inhibitor, zileuton, as well as still clinically tested, timapiprant and setitpiprant act directly on the synthesis of eicosanoid mediators or their signaling molecules and receptors. Biosynthesis of endocannabinoids (2-AG, AEA) interfere with eicosanoids metabolic pathways. 2-AG—2-Arachidonoyl-glycerol (endocannabinoid); AEA—arachidonyl-ethanolamide (endocannabinoid); COX—cyclooxygenase; Cyt—cytochrome; EET—epoxyeicosatrienoic acid; GC—glucocorticoids; HETE—hydroxyeicosatetraenoic acid; HPETE—hydroperoxyeicosatetraenoic acid; LOX—lipoxygenase; LTE_4—leukotriene; LTRA—leukotriene receptor antagonists; LX—lipoxin; PLA—phospholipase; PG—prostaglandin; and TX—thromboxane

the rate of parent-reported asthma symptoms at 6 years of age, however, without any effect on lung function or doctor-diagnosed asthma.[6,7] The majority of respiratory viruses are known to modify several major eicosanoid pathways, including the COX and the LOX pathways[8] (Figure 2). RV infection increases expression of 5-lipoxygenase (5-LOX), 5-lipoxygenase activating protein (FLAP), and cyclooxygenase-2 (COX-2), as well as the production of prostaglandins E_2 (PGE_2) and PGD_2 by the respective isomerases in human bronchial epithelial cells, with higher levels in asthmatic patients than in controls.[9] In addition, cysteinyl leukotriene (cysteinyl-LT) levels, 5-LOX-positive cells, and FLAP-positive cells in bronchoalveolar lavage fluid are increased in humans upon RV infection and correlate with the emergence of upper respiratory symptoms.[10] Infection with RV affects airway mucosal barriers and also the peripheral blood and distant tissues. PGE_2 plays an important role in optimal antibody synthesis, as COX inhibitors reduce antibody release by plasma cells, also in case of viral infections.[11,12] Healthy individuals experimentally infected with RV showed a suppressed serum neutralizing antibody response when treated with aspirin or acetaminophen.[13] Significant increase in COX-2 (PTGS2) expression and in COX-derived metabolites is a hallmark of RSV[14] and influenza virus infection.[15] Pharmacologic inhibition of the COX pathway decreased RSV-induced lung pathology, although this was not linked to a specific metabolite.[14,16] At a later stage of RSV infection there is an increase in LOX metabolites, which might promote appropriate resolution of infection-induced

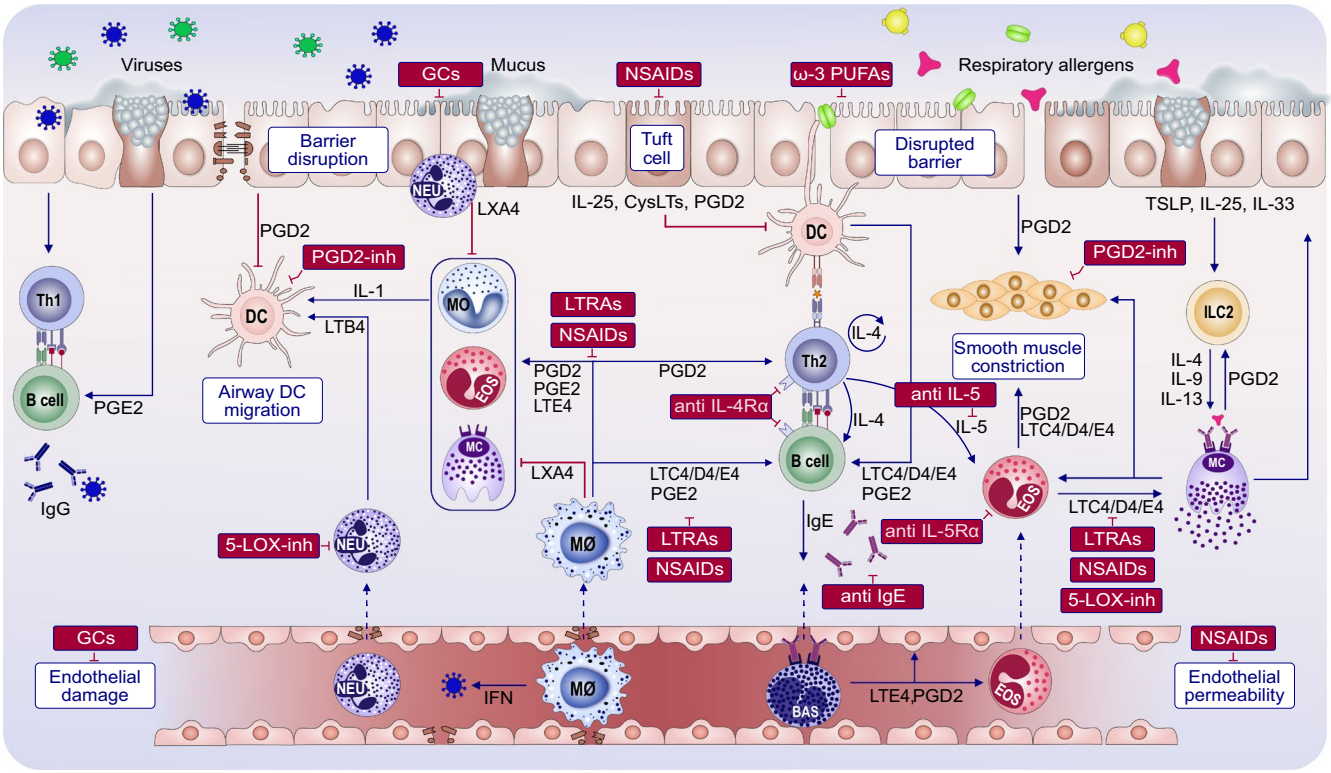

FIGURE 2 Eicosanoid pathways in viral infections and allergic inflammation of the respiratory airways are affected by several groups of medications. Eicosanoids are important immune mediators coordinating the inflammatory response to viral infections and allergen challenges between bronchial epithelial cells, airway-resident and airway-infiltrating immune cells. Several groups of drugs used in the treatment of allergic diseases and respiratory tract infections interfere with eicosanoid production and signaling pathways. Glucocorticoids (GCs) reduce the activity of phospholipase A_2 (PLA_2) and COX-2, therefore restricting both the upstream substrate for eicosanoid production and subsequent enzyme. NSAIDs block COX-1- and COX-2-mediated synthesis of prostaglandins by both bronchial epithelial cells and immune cells. This reduces tissue inflammation and alleviates the symptoms of infection, but at the same time affects the antiviral response. LTRAs block eicosanoid leukotriene signaling at the receptor level, reducing activation of granulocytes. Biologicals used in the treatment of allergic diseases (anti-IL-5, anti-IL-5Rα, anti-IL-4Rα, and anti-IgE) interfere with the eicosanoid signaling in a non-direct manner, by preventing undue activation of eosinophils and Th2 cells, as well as degranulation of basophils and mast cells. BAS—basophil; COX-1—cyclooxygenase 1; CysLTs—cysteinyl leukotrienes; DC—dendritic cell; EOS—eosinophil; GCs—glucocorticoids; IFN—interferon; IL—interleukin; LOX—lipoxygenase; LTE_4—leukotriene E4; LTRA—leukotriene receptor antagonists; LXA_4—lipoxin A4; MC—mast cell; MO—monocyte; Mθ—macrophage; NEU—neutrophil; NSAIDs—non-steroidal anti-inflammatory drugs; PLA2—phospholipase A2; PGD2—prostaglandin D2; PGE2—prostaglandin E2; PGD2-inh—prostaglandin D2 inhibitors; PUFA—polyunsaturated fatty acids; and TSLP—thymic stromal lymphopoietin

inflammation.[17] This resolution is impaired in 5-LOX and 15-LOX knockout mice upon RSV or pathogenic influenza strain infection. Moreover, in mice lacking 5-LOX, there is an upregulation of COX2 expression and aggravation of infection-induced lung pathology.[14,16] During influenza A infection, newly generated PGE_2 leads to the inhibition of type I interferon (IFN) production, inhibition of macrophage apoptosis, and subsequent increase in virus replication. *Ptges*$^{-/-}$ knockout mice, which do not produce PGE_2, or wild-type mice treated with PGE_2 type 2 (EP2) and type 4 receptor (EP4) antagonists demonstrated enhanced protection against lethal influenza infection.[18] PGE_2 also inhibits activation of the Nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome in human monocytes and macrophages, and COX pathway blocking increases inflammasome activation and mature Il-1β release. NLRP3 inflammasome activation can contribute to limiting viral replication at the early stages of infection, but in some instances, it may also lead to harmful hyperinflammation during late-stage infection.[19] Much less is known about PGD_2 and antiviral responses. However, it was shown that in aging mice there is an increase in PGD_2 in the lungs which correlates with the impaired migration of respiratory dendritic cells (DC) to lymph nodes, diminished T-cell responses, and more severe clinical disease in older mice infected with respiratory viruses, such SARS-CoV-1 and influenza.[20] Blocking PGD_2 function enhances DC migration, T-cell responses, and survival in the infected animals.[20] In summary, prostaglandins and other COX-dependent metabolites are involved in a complex way in the pathogenesis of respiratory viral infections and thus in virus-induced exacerbation of asthma. Therefore, the use of NSAIDs to alleviate symptoms of viral infections in general population and in patients with asthma should be re-evaluated with assessment of the effects of the timing of the administration, their selectivity, and the long-term effects.

3 | NSAIDS IN COVID-19

NSAIDs are used worldwide to alleviate symptoms of viral infections and inflammation, such as fever, cough, and pain. Since NSAIDs inhibit COX-1 and COX-2 and thus decrease the release of many downstream lipid mediators, such as various PGs, prostacyclin, and TXs, they have very broad effects on inflammation and immune responses, ranging from anti-inflammatory, immunosuppressive, and anti-thrombotic to pro-resolving (Figure 2).[1,21] Therefore, at the beginning of the COVID-19 pandemic, there were several concerns and uncertainties about the effects of NSAIDs on SARS-CoV-2 infection and the course of COVID-19.[22] They were suspected to alter the expression of angiotensin-converting enzyme 2 (ACE2), the main entry receptor for SARS-CoV-2 and/or modify viral replication.[23-26] In addition, they could be either harmful by impairing antiviral response and delaying resolution of inflammation[15,18,27,28] or be beneficial by dampening of hyperinflammation and cytokine storm[29,30] and preventing thrombosis[31,32] (Figure 3). Some of these concerns have now been addressed experimentally and epidemiologically, and several clinical trials have been initiated. Indeed, SARS-CoV-2 increases *PTGS2* (COX-2) gene expression in variety of cell lines, in mouse lungs and in primary human bronchial epithelial cells as well many eicosanoids and docosanoids are increased in the lungs of severe COVID-19 patients.[33-35] However, inhibition of the COX pathway by either ibuprofen (non-selective COX1/COX2 inhibitor) or meloxicam (more selective COX-2 inhibitor) did not change the expression of ACE2 in human cell lines (Calu-3 or Huh7.5) *in vitro* or in lungs, kidney, heart, or ileum of mice *in vivo*.[33] Similarly, both NSAIDs did not affect SARS-CoV-2 entry or its replication in the same human cell lines.[33] Aspirin also did not affect ACE2 or transmembrane serine protease 2 (TMPRSS2) expression in human nasal epithelium.[36] Meloxicam also did not prevent SARS-CoV-2-infection-induced weight loss in mice and did not change frequencies or activations status of alveolar macrophages, neutrophils, NK cells, Ly6C+ Mo/Mθ, $CD4^+$ T cells, $CD8^+$ T cells, and γδ T cells. However, meloxicam treatment decreased the amount of spike-specific IgM and IgG antibodies and their neutralizing capacities as well as decreased infection-induced levels of IL-6, CCL2, GM-CSF, CXCL10, IL-2, and TNF-α, suggesting that while meloxicam can impair humoral immune response against SARS-CoV-2 to some extent, it might also limit levels of proinflammatory cytokines.[33] In contrast, naproxen, which is a non-selective COX-1/COX-2 inhibitor, has been shown to bind to the nucleocapsid protein N of SARS-CoV-2, which led to inhibition of SARS-CoV-2 replication in VeroE6 cells and primary human bronchial epithelial cells and protected epithelium against SARS-CoV-2-induced barrier damage.[37] There were no analogous effects in similar experiments with paracetamol (acetaminophen, which may affect PG production in the brain or may act via its metabolite on the cannabinoid receptors),[38,39] or celecoxib (selective COX-2 inhibitor).[37] Naproxen is currently examined in the clinical trial in COVID-19

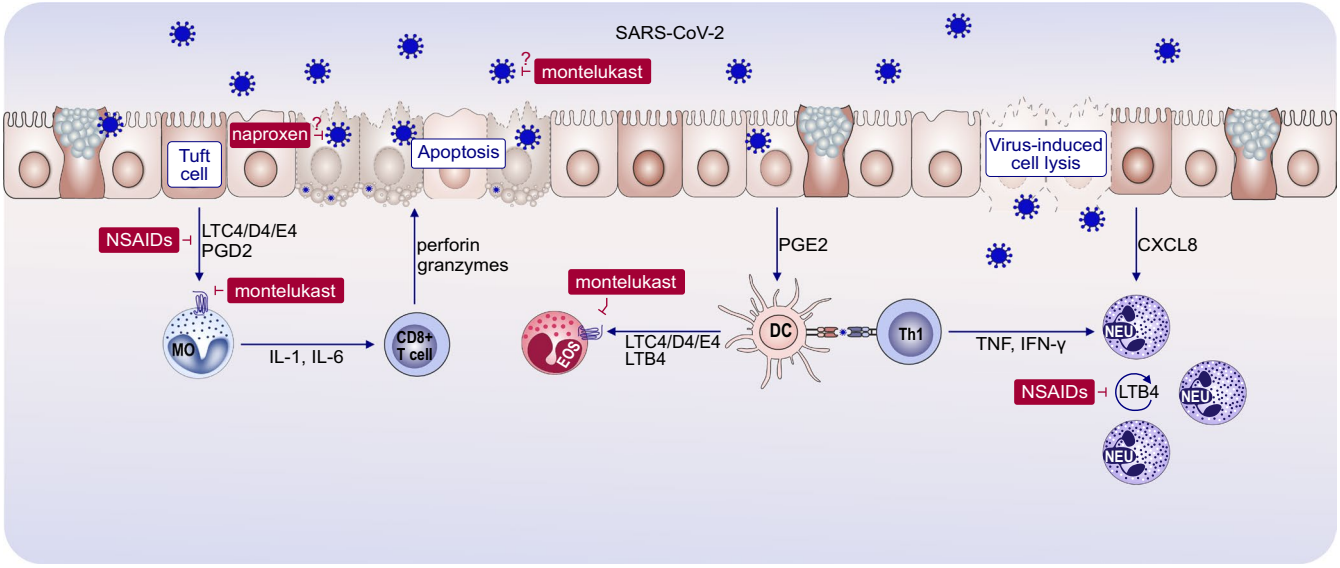

FIGURE 3 Non-steroidal anti-inflammatory drugs and leukotriene antagonists in SARS-CoV-2 infection. Increased levels of eicosanoids have been found in bronchoalveolar lavage fluid of patients with severe COVID-19, with predominance of prostaglandins and thromboxane. There are strong grounds to explore eicosanoid inhibition as a potential therapeutic target in SARS-CoV-2 infections. Prostaglandins amplify innate immune responses to pathogen- and damage-associated molecular patterns, enhance the cascade of proinflammatory cytokine release, activate Th1 and Th17 cells, and contribute to recruitment of macrophages and T cells. Moreover, studies in mouse adapted to SARS-CoV-2 infection showed that PGD_2 inhibition protected from severe disease. Despite the initial mixed reports on the use of NSAIDs in COVID-19, it has been concluded that these medications can be safely used to alleviate the symptoms of SARS-CoV-2 infection. This effect is attributed to the disruption of inflammatory circuits. Other effects of NSAIDs in COVID-19 are being investigated, and preliminary studies suggest that a non-selective NSAID naproxen could negatively influence SARS-CoV-2 replication. Furthermore, the efficacy of leukotriene antagonist montelukast is being evaluated in a series of clinical trials. The hypothesized mode of action in COVID-19 includes inhibition of leukotriene signaling, as well as direct antiviral effect (damage to the viral lipid membrane and genome), as reported for other viruses

(eudract_number:2020-001301-23; accessed 11.06.2021). So far, in various patient groups, it has been shown that usage of NSAIDs does not lead to the worse COVID-19 outcomes.[40] In a retrospective study of 403 confirmed cases of COVID-19, there were no differences in terms of mortality rate or need for respiratory support between patients who were taking ibuprofen or those who did not take any NSAIDs.[41] It was also confirmed in the large prospective cohorts that either acute or chronic use of NSAIDs was not associated with worse COVID-19 outcomes.[42-44] It was even shown that in patients, who were treated with aspirin or other NSAIDs due to the cardiovascular diseases, positive aspects of such therapies have been noted, including reduction of COVID-19 mortality.[31] This clinical observation is further supported by a study on COX-2 induction and PGE_2 overproduction in the human lung infected by SARS-CoV-2.[45] However, further basic in vitro, in vivo, and large clinical studies assessing the influence of NSAIDs on the pathogenesis and treatment of COVID-19 are still greatly needed.

4 | LEUKOTRIENE RECEPTOR ANTAGONISTS—NOVEL MECHANISMS OF ACTION

All clinically available LTRAs (montelukast, zafirlukast, and pranlukast) act on the cysteinyl leukotriene type 1 receptor ($CysLT_1$) and by competitive antagonism at this receptor are believed to be responsible for the control of airway inflammation, bronchoconstriction, and remodeling.[46-48] However, anti-inflammatory activity of LTRAs independent of $CysLT_1$ antagonism has been suggested. LTRAs reduced the eosinophil protease activity[49] and inhibited TNFα-[50] or UDP-mediated[51,52] cytokine expression, as well as NF-κB activation in human mononuclear[53] or epithelial cells[54] through processes that appear to be distinct from $CysLT_1$ antagonism. Although mechanisms of these non-$CysLT_1$-related LTRA activities are not fully understood, concentration-dependent inhibition of distinct receptors such as P2Y1, P2Y2, P2Y6, and GPR17 by LTRAs have been reported,[51,52,55] suggesting, at least for P2Y receptor, a non-competitive mechanism of action. Interestingly, it was also shown that LTRAs may have a potent inhibitory effect on 5-LOX activity (i.e., LT production)[52,56] and transport of LTs by the multidrug resistance protein ABCC4,[57] suggesting a much broader mechanism of action for these drugs than previously suspected. Indeed, non-$CysLT_1$-related mechanisms of LTRA might represent another level of variability in the response to treatment in patients with asthma and allergy. Some of these activities may be compound-specific or may depend on drug concentration (most non-$CysLT_1$-related effects required micromolar drug concentrations[51-53] in contrast to nanomolar levels needed for $CysLT_1$ antagonism[58-60]) or may depend on the presence of a particular inflammatory pathway in patients with asthma (allergy), and therefore, clinically significant effects of treatment may be observed in some, but not all, treated patients. It should be emphasized that initial clinical interventional studies of montelukast in asthma used doses up to 200 mg a day[61,62] showing greater lung function improvement than in subsequent studies using recommended dose of 10 mg,[63] suggesting that higher doses of currently known LTRAs or new compounds derived from this class of drugs may represent a novel strategy for finding more efficient therapy. The demonstration that the bronchoconstrictive actions of LTE_4 in asthma are solely mediated by the $CysLT_1$ receptor further supports that effects on other targets than the CysLT receptors may take place[64]

5 | PREDICTING RESPONSES TO LTRA THERAPY

Heterogeneous effects of LTRA therapy in asthma and allergic diseases have been reported in many studies. Although some genetic[65,66] and acquired factors have been suggested,[67] other reasons for this heterogeneity remain unclear. While currently no clinical characteristics or laboratory assay can reliably predict responses to LTRAs, the most plausible biomarker that could potentially serve as response predictor to LTRAs seems LTE_4 production. Urinary LTE_4 ($uLTE_4$) is a biomarker of total body cysteinyl-LT production,[1] associated with Type 2 asthma, asthma severity, exacerbations, and NERD.[68,69] Increased $uLTE_4$ to fractional exhaled nitric oxide (LTE_4:Fe_{NO}) ratio has been suggested to predict favorable response to LTRA therapy (montelukast) in asthmatic children,[70,71] but these observations have not been confirmed in adult patients. There is a considerable amount of evidence supporting the concept that some patients or clinical phenotypes seem sensitive to LTRAs, especially in a real-life setting, due to enhanced cysteinyl-LT production, better adherence to oral therapy or oral drug delivery. LTRAs have proven to be particularly effective in exercise-induced asthma,[72] asthma associated with allergic rhinitis,[73] NERD,[74] viral-induced wheezing episodes,[75] and patients having difficulties with inhaled therapy such as children and elderly.[76,77] Cigarette smoking while inhibiting steroid anti-inflammatory responses[78] increases cysteinyl-LT production,[79] leading to a greater response to montelukast in smokers with asthma, suggesting that LTRA could be more effective in treating such individuals.[80] In fact, asthmatic patients with smoking history above 11 pack-years showed more benefit with montelukast treatment than inhaled steroids.[81] Obesity is another potential risk factor for asthma development and efficacy of treatment. Interestingly, higher body mass index (BMI) is associated with increased LT production in asthmatics[82] and as therapeutic response to inhaled corticosteroids decreases with increasing BMI, response to montelukast remains unaffected,[83] suggesting LTRA therapy to be more effective in obese patients. The response to LTRA may also be associated with sex differences. The existence of a sex bias in LT biology is already suggested by the fact that many LT-related diseases including asthma, allergic rhinitis, rheumatoid arthritis, or NERD have a higher occurrence in women compared to men, pointing to more pronounced pathophysiological roles of LTs in females.[84,85] Furthermore, several observations suggest that female sex is associated with higher LT biosynthesis, while androgens seem to exert a suppressing role on

LT formation both in vitro and in vivo.[86-90] Although the clinical significance of these data is still to be confirmed, in a small prospective cohort study, montelukast showed superior effects on symptoms and lung function in women compared to men,[91] while a tendency for a better response to montelukast was evident in girls exposed to tobacco smoke.[92]

6 | LEUKOTRIENE MODIFYING DRUGS IN COVID-19 TREATMENT

Due to the involvement of complement, coagulation, and inflammation in COVID-19,[32,93,94] anti-inflammatory drugs have gained great interest as disease modifiers (Figure 3).[95] Already at the beginning of the COVID-19 pandemic, researchers suggested the use of the LTRA montelukast for treatment of COVID-19.[96-98] The reason for this early interest in LT-modifying drugs was on the one hand related to the viral cell entry via ACE2 receptors and the known inhibitory effect of montelukast on bradykinin-related airway response[99] and on the other hand to the fact that patients with severe COVID-19 develop an overwhelming state of inflammation that has been labeled COVID-19 cytokine storm syndrome (CSS).[32,100,101] Moreover, the most important cause of death in COVID-19 was recognized as the progressive respiratory failure with limited response to treatment together with hyperinflammation and hypoxia, quite similar to a severe acute respiratory distress syndrome (ARDS), which has been demonstrated to be characterized by an elevated level of LTs.[102] Of note, high levels of LTE_4 have been detected in bronchoalveolar lavage (BAL) of hospitalized patients with severe COVID-19,[34] as well as there is a shift in serum eicosanoids into the increase of 5-LOX products in such patients.[35] Indeed, specific benefits of montelukast, or other LTRAs, have been suggested in the situation of hyperinflammation and massive cytokine release[103] to reduce elevated levels of LPS-induced IL-6, TNF-α, and MCP-1 production in the peripheral blood MNCs of patients with asthma,[104] as well as to reduce levels of many cytokines and chemokines (IL-4, IL-5, IL-1β, TNF-α, RANTES, and IL-8) in nasal mucosa[105] possibly due to modulation of TNF-α-stimulated IL-8 expression through changes in NF-κB p65-associated histone acetyltransferase activity.[50] In addition to its anti-inflammatory properties in humans, *in silico* studies also suggested, but still to be demonstrated, a direct antiviral effect by showing a high-affinity binding of montelukast to the terminal end of the virus' main protease enzyme needed for viral protein assembly.[106]

Thus, with increasing understanding of disease mechanisms, LTRAs have been also considered for treatment of COVID-19. Indeed, in a small retrospective study on COVID-19-hospitalized subjects, patients receiving montelukast had fewer episodes of confirmed COVID-19 or experienced significantly fewer events of clinical deterioration compared to patients not receiving montelukast.[107,108] These lipid mediators might not only contribute to inflammation and lung pathologies associated with COVID-19, but can also be involved in thrombosis, fibrosis, neuronal damage, and cardiovascular disease.[97,109,110] Interestingly, we have recently demonstrated that montelukast inhibits platelet activation and microvesicles release induced by plasma from COVID-19 patients, as well as the formation of circulating monocyte- and granulocyte-platelet aggregates.[111] All these data suggest the repurposing of montelukast as a possible auxiliary treatment for COVID-19 syndrome. Accordingly, since May 2020 a series of clinical trials involving montelukast have been registered (https://clinicaltrials.gov). However, not only antagonism of the CysLT receptors could be beneficial for patients with COVID-19, but interventions targeting LT biosynthesis, using, for example, Zileuton, might represent promising targets, specifically at the turning point from a mild to critical disease course.[112]

7 | PGD_2 RECEPTOR ANTAGONISTS

In sensitized subjects, PGD_2 is initially released by allergen-triggered mast cells and plays a key role in the sequelae of the allergic response. Its proinflammatory effects are mediated through the interaction with G-protein-coupled receptors (GPCR): DP1, thromboxane (TP), and chemoattractant-homologous receptors (CRTH2 or DP2).[113] Apart from its broncho- and vaso-active properties in allergic airway disease, PGD_2 also acts as an important link between the allergen-induced early (EAR) and late phase allergic response (LAR) through the interaction with the DP2-receptors on key effector cells. DP2-receptors are expressed on immune (ILCs, Th2), inflammatory (eosinophils, basophils), and structural (epithelial) cells and involved in the recruitment and activation of these cells as well as the subsequent release of Th2-cytokines during the LAR.[113-116] Therefore, DP2 (CRTH2) antagonists have been initially aimed for the treatment of allergic airway disease (allergic rhinitis, asthma).[117,118]

In two proof-of-concept studies in (unphenotyped) allergic asthmatics, DP2 (CRTH2) antagonists (timapiprant and setipiprant, respectively) showed only modest reduction (approx. 25%) in the allergen-induced LAR[119,120] while no convincing effects were observed on the allergen-induced changes in T2 biomarkers (blood eosinophils, FeNO)[120] with only a minimal reduction in sputum eosinophils post-allergen.[119] In addition, there was no decrease in the EAR in either study. The (relative) lack of protection against allergen-induced airway responses may (partly) consist with the fact that even with effective DP2-blockade, an allergen-triggered mast cell (lacking DP2)[121] mediator release (histamine, PGD_2, cysteinyl-LTs) may still occur which is capable of causing an EAR and/or an LAR[122,123] and therefore, especially in allergic asthma, a combined blockade of, for example, DP2 ± DP1 ± TP ± cysteinyl-LT-R might provide a superior protection.

In line with this reasoning—and despite prior evidence of superior efficacy in phase 2B studies of patients with an allergic (T2-) profile (atopy ± eosinophils ≥250/mcL)[124,125]—several DP2 (CRTH2) antagonists (e.g., setipiprant, fevipiprant) failed in phase 3 clinical trials of allergic airway disease.[125] More recently, DP2-blockade has been associated with the reduction in airway smooth muscle mass by decreasing airway eosinophilia and the recruitment of myofibroblasts and fibrocytes.[126] Therefore, with several clinical trials still

ongoing, (add-on) DP2-blockade may show efficacy in more severe T2 asthma[127] and related conditions based on its anti-inflammatory and disease-modifying potential.[126,128]

Respiratory viruses (e.g., RSV) represent other important triggers of chronic inflammatory airway disease capable of activating the PGD_2/DP2 receptor-mediated pathway, thereby eliciting a "non-allergen-induced" T2-immune response through airway epithelial cells and innate immune cells.[129] Indeed, RSV has been associated with upregulation of the PGD_2/DP2 pathway and increased PGD_2 levels both in experimental and in clinical studies, while DP2-blockade alone or combined with DP1 agonism showed protective potential in preclinical studies.[130] Therefore, selective targeting of PGD_2 receptors has been postulated to protect against respiratory viral infections, and more recently, including SARS-CoV-2.[131] Presently, this hypothesis awaits clinical evidence. In addition, the potent bronchoconstrictive actions of PGD_2 and other constrictive prostanoids in human airways call for trials with TP receptor antagonists in patients with asthma[132]

8 | CANNABINOIDS IN ASTHMA, ALLERGIC DISEASES, AND VIRAL INFECTIONS

The human endogenous cannabinoid system (ECS) is involved in many physiological processes. It consists of the cannabinoid receptors (CBRs), the endogenous ligands (anandamide (AEA) and 2-arachidonoylglycerol (2-AG)), and the proteins related to their synthesis and degradation.[133] Cannabinoid receptor 1 (CB1) and 2 (CB2) are the main CBRs. CB1 is largely expressed in the central nervous system but also in peripheral tissues and immune cells. CB2 is mainly expressed in immune cells but also in other cell types such as progenitor neurons.[134,135] The biosynthesis and inactivation of endocannabinoids involve several enzymes. AEA can be synthetized by the hydrolysis of its precursor N-acyl-phosphatidylethanolamine (NAPE) by NAPE-hydrolyzing phospholipase D (NAPE-PLD). Alternative pathways involving other phospholipases have been described. AEA can be also obtained from the reverse reaction of fatty acid amide hydrolase (FAAH) by the conjugation of ethanolamine and AA. The main pathway for the synthesis of 2-AG is the hydrolysis of AA-containing 1,2-diacylglycerol (DAG) species by DAG lipase-α or β.[133,136] Endocannabinoids are rapidly metabolized. The hydrolysis of AEA is mediated by FAAH, whereas 2-AG is hydrolyzed by monoacylglycerol lipase (MGL). The resulting products of AEA and 2-AG degradation are AA, and ethanolamine and glycerol, respectively (Figure 4)..[133,136] Moreover, endocannabinoids are susceptible to be metabolized by eicosanoid biosynthetic enzymes including COX2, 12-LOX, 15-LOX, and P450.[136] FAAH and MGL are considered promising therapeutic targets for the treatment of several disorders, including inflammation. Pharmacological inhibitors of FAAH and MGL increase the levels of AEA and 2-AG, prolonging their anti-inflammatory effects, and decrease AA levels.[137,138] The NSAIDs that inhibit COX2 also enhance endocannabinoid levels and reduce AEA- and 2-AG-derived prostaglandins.[139,140] In addition, some NSAIDs such as ibuprofen can influence the endocannabinoid levels by inhibiting FAAH (Figure 4).

The role of cannabinoids in allergic diseases is still a bit controversial.[141] Sukawara et al demonstrated that endocannabinoids limited mast cell maturation and activation in human airway mucosa and skin through CB1.[142,143] Tetrahydrocannabinol (THC) and cannabidiol (CBD) attenuated airway allergic inflammation, decreased cytokine production, cell infiltration, mucus secretion, and bronchial hyperresponsiveness in mice.[144-146] Similarly, the synthetic agonist CP55,940 induced lung protection in ovalbumine (OVA)-induced asthma guinea pig models via CB1 and CB2.[147] In keratinocytes, CB1 prevented transepithelial water loss and skin inflammation, cell infiltration and cytokine production in atopic dermatitis mouse model.[148] Anandamide and different CB1 agonists also accelerated skin barrier recovery and reduced proinflammatory cytokine production and cell recruitment.[149,150] Several cannabinoids have also shown a protective role in allergic contact dermatitis by reducing inflammatory responses.[151-153] CB1 activation may also induce bronchodilation in the airways.[147,154] In human bronchial epithelial cells, the synthetic agonist WIN55212-2 restored the epithelial barrier disruption induced by RV.[155] In addition, WIN55212-2 decreased the immediate anaphylactic reaction in a mouse model of peanut allergy and promoted the generation of allergen-specific regulatory T cells.[156] Currently, different studies suggest the therapeutic potential of cannabinoids in COVID-19 pandemic.[157-159] In contrast, Frei et al showed that CB2 activation enhanced migratory responsiveness of eosinophils in an OVA-asthma mouse models.[160] Accordingly, the lack of CB2 decreased allergic inflammation in asthma and dermatitis mouse model.[161] This result correlated with increased number of NK cells and reduced number of ILC2s in the lung of CB2 knockout mice, demonstrating that NK cells are negative regulators of ILC2s.[162] Interestingly, it has been described that mRNA expression levels of CB1 are upregulated in tonsils and peripheral blood of patients with allergic rhinitis, atopic dermatitis, and food allergy, but the functional relevance remains unknown.[163] These studies suggest that the ECS could be explored as a potential therapeutic target in the treatment of asthma, allergic and skin diseases, and viral infections.

9 | THE EFFECT OF T2-TARGETED BIOLOGICALS ON EICOSANOIDS

Ample evidence from clinical trials showing effectiveness of drugs targeting T2-inflammation (targets include IgE and the cytokines IL5, IL4, and IL13) on asthma exacerbations, as well as improvements in symptoms and disease severity in chronic rhinosinusitis with nasal polyps (CRSwNP),[164,165] underscored the involvement of T2-inflammation in these conditions.[166,167] As mentioned above, the majority of asthma exacerbations are precipitated by respiratory viruses (esp. RSV and RV),[168] while in sensitized subjects, allergen exposure may enhance virally triggered exacerbations due to synergistic interaction through joint mechanisms including the

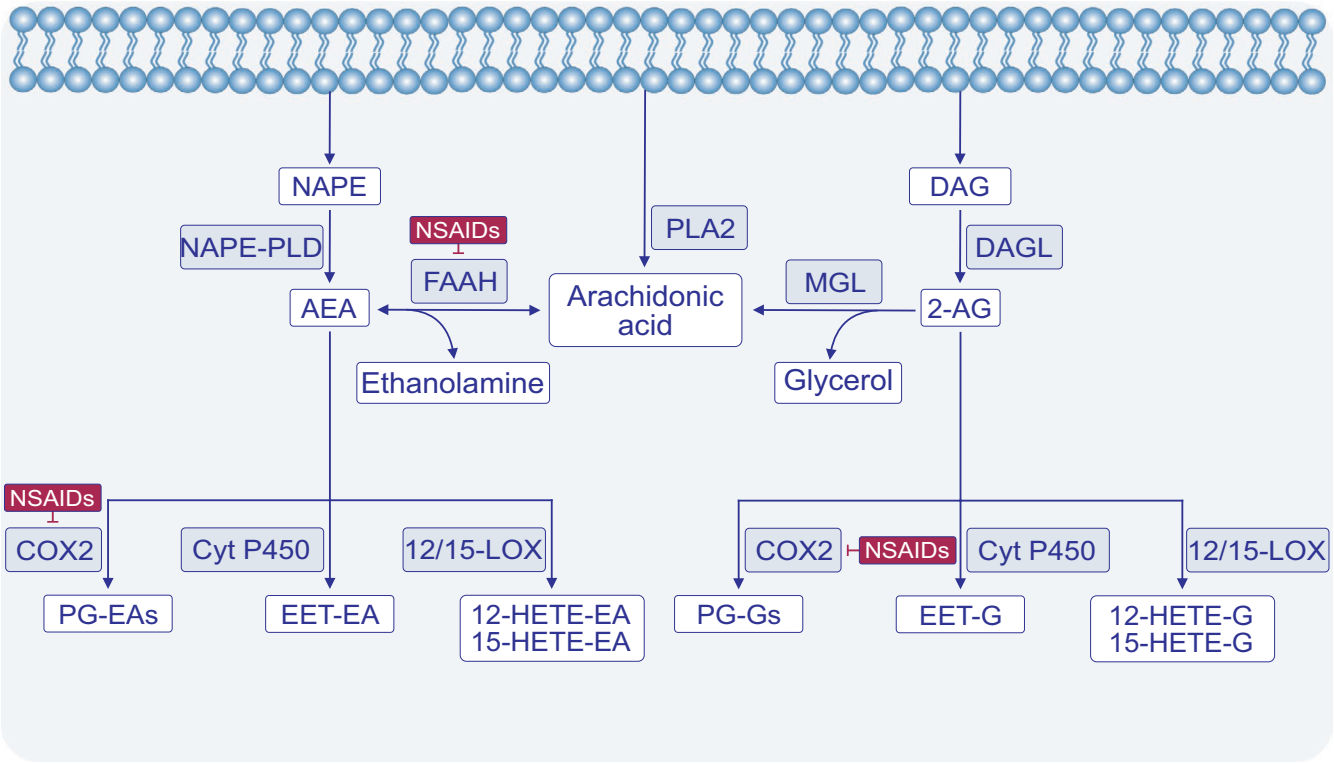

FIGURE 4 Interactions of endocannabinoid with arachidonic acid metabolism and effects of non-steroidal anti-inflammatory drugs (NSAIDs). Main endocannabinoids in humans include arachidonyl-ethanolamide (AEA) and 2-arachidonoyl-glycerol (2-AG). AEA can be obtained from N-acyl-phosphatidylethanolamine (NAPE) via hydrolysis or by conjugation of ethanoloamine and arachidonic acid (AA). AEA can be also hydrolyzed to AA by the fatty acid amide hydrolase (FAAH). FAAH might be inhibited by NSAIDs. 2-AG comes from diacylglycerol (DAG) through the actions of DAG lipase (DAGL). 2-AG can be also hydrolyzed by monoacylglyserol lipase (MGL) to AA. Endocannabinoids also metabolized by eicosanoid biosynthetic enzymes including COX2, 12-LOX, 15-LOX, and cytochrome P450. The NSAIDs inhibiting COX2 can enhance endocannabinoid levels and reduce AEA- and 2-AG-derived prostaglandins. COX—cyclooxygenase; Cyt—cytochrome; EET—epoxyeicosatrienoic acid; HETE—hydroxyeicosatetraenoic acid; LOX—lipoxygenase; PLA—phospholipase; and PG—prostaglandin

T2-inflammatory pathway.[168-171] Both viral and allergen-triggered pathways include several inflammatory and immune (effector) cells, such as mast cells, basophils, Th2 cells, ILCs, macrophages, neutrophils, and eosinophils. Many of these cells are capable of releasing eicosanoids upon activation and/or possess one or more eicosanoid receptors,[172] thus contributing to the exacerbation and its sequelae (e.g., bronchoconstriction, airway inflammation, and bronchial hyperresponsiveness).[173] In CRSwNP, the T2-inflammatory pathway is also triggered by several stimuli such as viruses, bacteria, and allergens, which stimulate inflammatory cell- and cytokine-mediated pathomechanisms in the nasal and paranasal mucosa.[167]

Although *in vitro* data indicate that biologicals may influence eicosanoid pathways in mast cells and basophils,[174] so far there are no published data on direct effects of T2-targeted biologicals on the synthesis or release of eicosanoids in humans *in vivo* (Figure 5). However, it makes sense that, by blocking pathways and cells (esp. mast cells, basophils, eosinophils, and neutrophils) responsible for the release of these proinflammatory mediators, may consequently also reduce eicosanoid levels. In addition, previous evidence from clinical studies in asthma showed (partial) reduction of both allergen- and virus-induced airway responses and asthma exacerbations by selective eicosanoid antagonists.[48,119,120,175-177] Besides, clinical studies on biologicals in CRSwNP also included a representative cohort of patients with NERD and also found a good clinical response[164] and a reduced T2-biomarker profile in this subpopulation.[178] However, so far there are no data on the direct effect of T2 biologicals on the individual eicosanoids nor head-to-head studies comparing biologicals with selective eicosanoid blockers or combinations.

10 | NSAID-EXACERBATED RESPIRATORY DISEASE (NERD). SELECTIVITY OF NSAIDS

NERD, also called AERD-aspirin-exacerbated respiratory disease or AIA-aspirin-intolerant asthma, is a phenotype of asthma recognized in 5 to 25% asthmatics. It is characterized by a non-immunological hypersensitivity to low doses of NSAIDs and a cross-reactivity (a multi-responder phenotype). Profound changes in biosynthesis of eicosanoids comprise overproduction of cysteinyl-LTs, excreted in urine as LTE_4.[179,180] Some patients have higher excretion of LTE_4 also during a stable period of NERD.[74,181-183] It is debatable, which

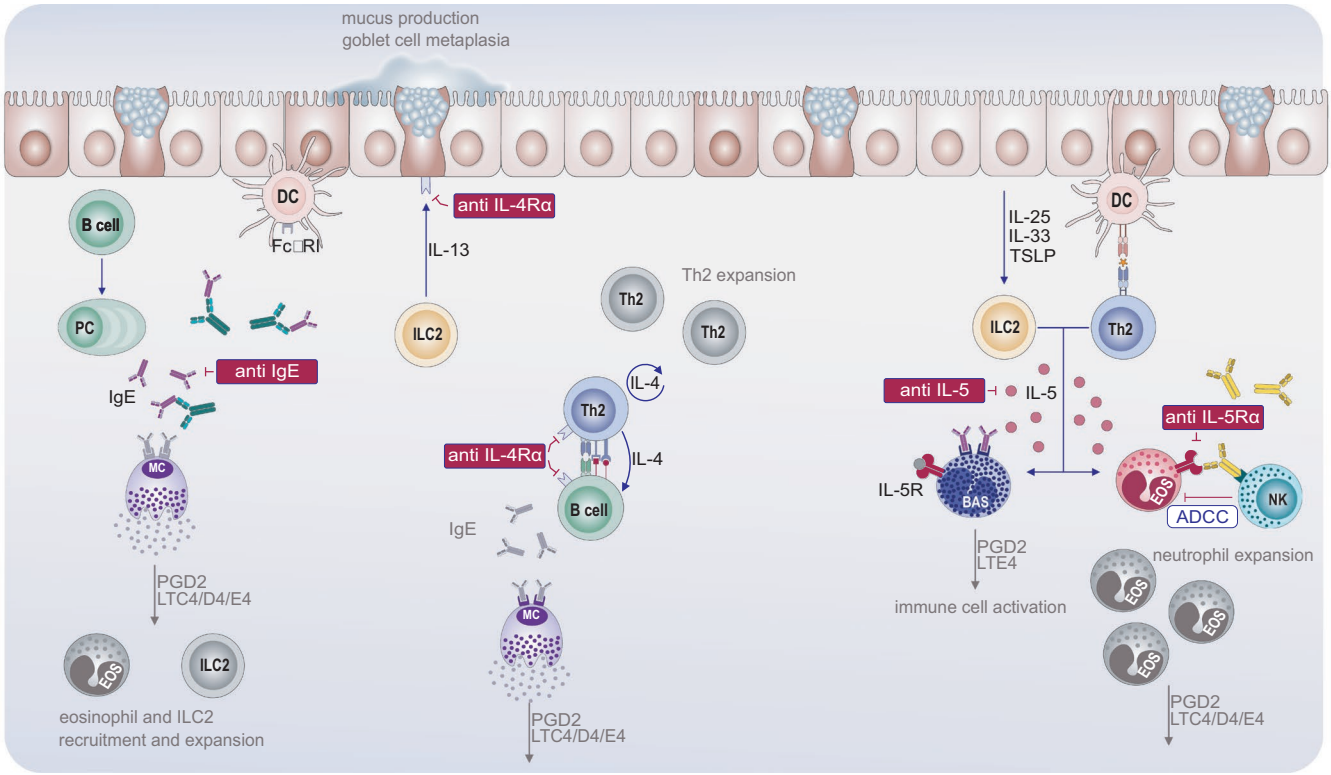

FIGURE 5 Effect of biologicals used in the treatment of allergic diseases on eicosanoid pathways. Biologicals have revolutionized therapeutic algorithms for patients with the most severe form of allergic diseases. Currently, 5 monoclonal antibodies have been approved for the treatment of severe asthma. Their use has been associated with a decrease in the concentration of proinflammatory lipid mediators. This is most probably an indirect effect of inhibition of immune cells which are the main eicosanoid producers in allergic inflammation. Omalizumab (anti-IgE) binds to free IgE and inhibits their binding to IgE receptors, which results in a downregulation of FcεRI expression on mast cells, basophils, and dendritic cells. This leads to a significant decrease in biosynthesis and release of proinflammatory eicosanoids from these cells, and prevents expansion of eosinophils and ILC2. Dupilumab (anti-IL-4Rα) binds to the α subunit of the IL-4 receptor, which is shared by IL-4 and IL-13 receptor complexes. Therefore it blocks the effect of these cytokines on cells contributing to type 2 immune reaction. This results in an inhibition of IgE production, mast cell activation and eicosanoid production, goblet cell metaplasia, and mucus production. Mepolizumab, reslizumab (anti-IL-5), and benralizumab (anti-IL-5Rα) block IL-5 activity on different levels, therefore inhibiting the maturation, activation, and proliferation of eosinophils, as well as basophil activation. Monoclonal antibodies targeting IL-5Rα moreover lead to antibody-dependent cell-mediated cytotoxicity of NK cells against eosinophils and basophils, vast producers of proinflammatory eicosanoids such as prostaglandin D_2 and cysteinyl leukotrienes. While no direct effect of biologicals on eicosanoid biosynthesis has been reported, these medicines disrupt the cascade of immune events leading to type 2 inflammatory responses and the concomitant overproduction of proinflammatory lipid mediators

cells produce cysteinyl-LTs in NERD. Since overproduction of PGD_2 and increase of histamine concentration accompany symptoms of NERD, these could be mast cells. However, eosinophils in NERD overexpress leukotriene C4 synthase (LTC4S), thus can contribute to the symptoms and concurrent release of eosinophils cationic protein was observed. PGE_2 plays a key role in NERD, where both decreased production of PGE_2 and reduced EP_2 expression were observed.[180,184] When PGE_2 is further decreased, it leads to mast cell activation and bronchoconstriction because it removes the stabilizing effect of PGE_2 on mast cell mediator release.[132] Accordingly, inhalation of PGE_2 before aspirin challenge prevented reduction in pulmonary function and mast cell activation.[185] However, inhibition of PGE_2 biosynthesis by NSAIDs is difficult to measure, since this prostaglandin is produced by most cells of the body. Interestingly, patients with NERD have also an imbalance in pro-resolving lipoxin A_4 (LXA_4) that may contribute to the increased severity of this particular asthma endotype.[186] The minimal dose triggering bronchial constriction and extra bronchial symptoms (cutaneous flush, nasal obstruction, irritations of conjunctiva) varies across patients, but generally it reflects NSAID potency to inhibit cyclooxygenase-1 isoenzyme (COX-1).[187,188] Highly selective inhibitors of COX-2 like coxibs (e.g., celecoxib, etoricoxib)[189] are well tolerated in most NERD patients, whereas preferential COX-2 inhibitors (nimesulide, meloxicam) can trigger symptoms at high doses[190] (Table 1). Diclophenac, ketorolac, ibuprofen, naproxen, indomethacin, or pyrazolone derivatives inhibit both COX-2 and COX-1,[191] therefore are contraindicated in NERD. Acetylsalicylic acid is more potent inhibitor of COX-1 than COX-2.[189,192] This was the first NSAID ever reported to trigger symptoms in asthmatics. Paracetamol (acetaminophen), with an unclear effects on prostanoids biosynthesis including possible inactivation of brain cyclooxygenases by a non-substrate mechanism, is tolerated by the vast majority of NERD patients unless given in very high doses.[39]

TABLE 1 Molecular targets and selectivity of drugs affecting eicosanoid pathways

Drug	Group	Target	Remarks	References
Ketoprofen	NSAID	COX-1 >> COX-2		204
Aspirin	NSAID	COX-1 >> COX-2		192
Naproxen	NSAID	COX-1, COX-2		204
Ibuprofen	NSAID	COX-1, COX-2		204
Diclofenac	NSAID	COX-1, COX-2		191
Ketorolac	NSAID	COX-1, COX-2		205
Indomethacin	NSAID	COX-1, COX-2		206
Dipyrone (metamizole)	NSAID	COX-1, COX-2		207
Piroxicam	NSAID	COX-2 > COX-1		192
Meloxicam	NSAID	COX-2 >> COX-1		192
Nimesulide	NSAID	COX-2 >> COX-1		189
Celecoxib	NSAID	COX-2 >> >COX-1		189
Etoricoxib	NSAID	COX-2 >> >COX-1		189
Paracetamol (acetaminophen)	Related to NSAIDs	COX-1, COX-2-non-substrate mechanism		38,39
Montelukast	LTRA	CysLTR1	Additional immunomodulatory properties have been suggested	46
Zafirlukast	LTRA	CysLT1		46
Pranlukast	LTRA	CysLT1		46
Zileuton	Leukotriene synthesis inhibitor	5-LOX		208
Fevipiprant	Prostaglandin receptor antagonist	DP2	Phase 3 clinical trials	209
Asapiprant	Prostaglandin receptor antagonist	DP1	Phase 2 clinical trials	ClinicalTrials.gov Identifier: NCT04705597
Laropiprant	Prostaglandin receptor antagonist	DP1	Temporarily approved in Europe as a component of a hypolipidemic drug	210
Vidupiprant	Prostaglandin receptor antagonist	DP2 > DP1	Phase 2 clinical trials	ClinicalTrials.gov Identifier: NCT01018550

11 | EICOSANOIDS IN DRUG ALLERGY

Most of the information available on the role of eicosanoids in allergy and related diseases concerns NERD.[193,194] This fact can be explained because it was the first clinical phenotype in which a link between NSAIDs pharmacological activity and the inhibition of PGE_2 synthesis by blocking COX-1 and the subsequent increase in cysteinyl-LTs release was established.[195] Nevertheless, some data are also available for cutaneous NSAID-induced cross-hypersensitivity. Thus, increased LTE_4 and 9α,11β-PGF_2 urinary levels have been described for NERD[196-199] and for NSAID-induced acute urticaria/angioedema (NIUA).[199]

For NSAID-exacerbated cutaneous disease (NECD), contrasting results have been found regarding eicosanoids levels at basal state. Thus, Di Lorenzo et al. did not report baseline differences for LTE_4 in patients with chronic urticaria and hypersensitivity to acetylsalicylic acid (ASA, aspirin) or food additives,[200] and no variations at basal state were reported for LTE_4 and 9α,11β-PGF_2 by two other independent studies.[197,199] However, Mastalerz et al. reported increased LTE_4 levels in NECD patients with a positive aspirin challenge with respect to those with a negative aspirin challenge, and with no changes found for 9α,11β-PGF_2.[201] It has been recently published that NIUA and NECD showed similar increased levels in both LTE_4 and 9a,11b-PGF_2 within the first 3 hours following a positive aspirin challenge; however, after this time interval, these mediators showed different behaviors, being such levels long-lasting in NECD.[199] In spite of these differences being not statistically significant, the reasons explaining the existence of these particular profiles are at present unknown although they may be due to the presence of additional factors in NECD, which could include sensitization to autoantibodies or the existence of histamine-releasing factors.[199]

Data on the role of eicosanoids beyond NSAIDs-hypersensitivity are scarce. However, a potential role for cysteinyl-LTs was proposed in adverse reactions to non-ionic contrast media. Thus, iopromide and iotrolan induced a significant increase of cysteinyl-LTs *in vivo*, with no changes in preformed mediators levels.[202] However, a previous study showed the heterogeneity of the effects of contrast media on mediator release, showing an increase in histamine and tryptase release from different human cells without changes in LTE_4 or PGD_2 levels.[203]

12 | CONCLUSIONS AND UNMET NEEDS

NSAIDs, LT modifiers, and biologicals are used every day in clinical practice in treatment of viral infections and common respiratory or allergic diseases. Although a significant progress has been made in our understanding how these medications act and how they affect eicosanoid pathways, there are still no sufficient data available to fully address all issues important for prediction of their activities affecting immune response and estimation of their clinical efficacy. This consensus report summarizes up to date knowledge in this complex area and identifies major knowledge gaps and unmet needs to be addressed in the future.

12.1 | Unmet needs

- Assessment of NSAIDs role in alleviating symptoms of viral infections in general population and in patients with asthma/ allergy with the strong emphasis on the timing of its administration, their selectivity, and long-term effects.
- Further basic in vitro, in vivo, and large clinical studies assessing NSAIDs influence on the pathogenesis and treatment of COVID-19 are greatly needed.
- Understanding molecular and cellular mechanisms of eicosanoids activity in immune response with focus on balance between pro- and anti-inflammatory properties.
- Characterization of emerging sub-phenotypes, and sub-endotypes of allergic diseases (asthma, rhinitis, and NERD) and potential biomarkers for the more effective therapy using eicosanoid pathway modifying drugs (NSAIDs, LTRA, and CRTH2 antagonists)
- Evaluation of how the effectiveness of new biologicals for the treatment of allergic diseases relates to the eicosanoids.
- Re-assessment of the effects of prostanoids in allergic and asthmatic reactions in humans by targeted intervention studies with selective inhibitors of receptors or tissue-specific synthases.
- Development and testing of novel treatment modalities targeting lipid mediators (eicosanoids) and their receptors.

CONFLICT OF INTEREST

MiSo has received research grants from the Swiss National Science Foundation, GlaxoSmithKline, Novartis, and AstraZeneca speaker fee. ZD acted as a director respiratory/allergy for QPS-NL (2012-2020); she has received consulting fees from ALK, Antabio, GSK, Sanofi-Genzyme, QPS-NL; has participated in the speaker's bureaus of Boehringer Ingelheim, Sanofi-Genzyme; she serves in EUFOREA as an Asthma Expert Panel Chair. OsPa has received fees for lectures and/or participation in Advisory Boards from Allergy Therapeutics, Amgen, AstraZeneca, Diater, GSK, Inmunotek SL, Novartis, Sanofi-Genezyme, Regeneron, and Stallergenes. OP has received research grants from Inmunotek SL and Novartis SL. CA has received research grants from the Swiss National Science Foundation, Christine Kühne-Center for Allergy Research and Education, European Commission Horizon's 2020 Framework Programme "CURE," Novartis Research Institutes, GlaxoSmithKline and AstraZeneca. He took part in the advisory board and received research grants from GlaxoSmithKline, Sanofi/Regeneron, SciBase, and Novartis. He is the editor in chief of Allergy. LOM is a consultant to PrecisionBiotics and has received research funding from GSK and Chiesi. LOM has participated in speaker's bureau for Nestle, Nutricia, Reckitt, and Abbott. MJ has received consulting fees (ALK-Abello, Stallergenes-Greer, Takeda, Zentiva); honoraria for lectures, presentations (ALK-Abello, Stallergenes-Greer, Takeda, Zentiva, Mundipharma, AstraZeneca, SOBI, Chiesi, CSL Behring, Novartis, Benela, Pfizer, Viatris); support for attending meetings and/or travel (ALK-Abello, Stallergenes-Greer, Takeda, Novartis, Sanofi Pasteur) and honoraria for participation on Advisory Boards (ALK-Abello, Stallergenes-Greer, Chiesi, Novartis, SOBI, Pfizer, Sanofi Genzyme/Pasteur). OIPh reports grants and personal fees from ALK-Abelló, grants and personal fees from Allergopharma, grants and personal fees from Stallergenes Greer, grants and personal fees from HAL Allergy Holding B.V./HAL Allergie GmbH, grants and personal fees from Bencard Allergie GmbH/Allergy Therapeutics, grants and personal fees from Lofarma, grants from Biomay, grants from Circassia, grants and personal fees from ASIT Biotech Tools S.A., grants and personal fees from Laboratorios LETI/LETI Pharma, personal fees from MEDA Pharma/MYLAN, grants and personal fees from Anergis S.A., personal fees from Mobile Chamber Experts (a GA2LEN Partner), personal fees from Indoor Biotechnologies, grants and personal fees from GlaxoSmithKline, personal fees from Astellas Pharma Global, personal fees from EUFOREA, personal fees from ROXALL Medizin, personal fees from Novartis, personal fees from Sanofi-Aventis and Sanofi-Genzyme, personal fees from Med Update Europe GmbH, personal fees from streamedup! GmbH, grants from Pohl-Boskamp, grants from Inmunotek S.L., personal fees from John Wiley and Sons, AS, personal fees from Paul-Martini-Stiftung (PMS), personal fees from Regeneron Pharmaceuticals Inc., personal fees from RG Aerztefortbildung, personal fees from Institut für Disease Management, personal fees from Springer GmbH, personal fees from AstraZeneca, personal fees from IQVIA Commercial, personal fees from Ingress Health, outside the submitted work; and member of EAACI Excom, member of ext. board of directors DGAKI; coordinator, main or co-author of different position papers and guidelines in allergology and allergen-immunotherapy. SED has received consultation fees from AZ, GSK, Merck, Novartis, Regeneron, Sanofi, Teva; has participated in the speaker's bureaus of AZ, GSK, Sanofi. Other authors do not have any COI to declare.

AUTHORS' CONTRIBUTIONS

MiSo and GW led the Task Force and supervised the project. MiSo, GER, ZD, EU, JS, ZL, FS, AA, OP, CA, LOM, MJ, OP, MJT, MS, SED, and GW conceptualized the project, reviewed the literature, wrote different sections of the manuscript, and edited the manuscript.

ORCID

Milena Sokolowska https://orcid.org/0000-0001-9710-6685
G Enrico Rovati https://orcid.org/0000-0002-8788-9783
Zuzana Diamant https://orcid.org/0000-0003-0133-0100
Eva Untersmayr https://orcid.org/0000-0002-1963-499X
Florentina Sava https://orcid.org/0000-0001-8936-3542
Oscar Palomares https://orcid.org/0000-0003-4516-0369
Cezmi Akdis https://orcid.org/0000-0001-8020-019X
Liam O'Mahony https://orcid.org/0000-0003-4705-3583
Milos Jesenak https://orcid.org/0000-0001-7976-2523
Oliver Pfaar https://orcid.org/0000-0003-4374-9639
María José Torres https://orcid.org/0000-0001-5228-471X
Grzegorz Woszczek https://orcid.org/0000-0003-0675-085X

REFERENCES

1. Sokolowska M, Rovati GE, Diamant Z, et al. Current perspective on eicosanoids in asthma and allergic diseases: EAACI Task Force consensus report, part I. *Allergy*. 2021;76(1):114-130.
2. Sheehan WJ, Mauger DT, Paul IM, et al. Acetaminophen versus Ibuprofen in Young Children with Mild Persistent Asthma. *N Engl J Med*. 2016;375(7):619-630.
3. Papadopoulos NG, Christodoulou I, Rohde G, et al. Viruses and bacteria in acute asthma exacerbations–a GA(2) LEN-DARE systematic review. *Allergy*. 2011;66(4):458-468.
4. Turunen R, Koistinen A, Vuorinen T, et al. The first wheezing episode: respiratory virus etiology, atopic characteristics, and illness severity. *Pediatr Allergy Immunol*. 2014;25(8):796-803.
5. Christensen A, Kesti O, Elenius V, et al. Human bocaviruses and paediatric infections. *Lancet Child Adoles Health*. 2019;3(6):418-426.
6. Simoes EA, Carbonell-Estrany X, Rieger CH, et al. The effect of respiratory syncytial virus on subsequent recurrent wheezing in atopic and nonatopic children. *J Allergy Clin Immunol*. 2010;126(2):256-262.
7. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med*. 2013;368(19):1791-1799.
8. McCarthy MK, Weinberg JB. Eicosanoids and respiratory viral infection: coordinators of inflammation and potential therapeutic targets. *Mediators Inflamm*. 2012;2012:236345.
9. Jakiela B, Gielicz A, Plutecka H, et al. Th2-type cytokine-induced mucus metaplasia decreases susceptibility of human bronchial epithelium to rhinovirus infection. *Am J Respir Cell Mol Biol*. 2014;51(2):229-241.
10. Seymour ML, Gilby N, Bardin PG, et al. Rhinovirus infection increases 5-lipoxygenase and cyclooxygenase-2 in bronchial biopsy specimens from nonatopic subjects. *J Infect Dis*. 2002;185(4):540-544.
11. Bancos S, Bernard MP, Topham DJ, Phipps RP. Ibuprofen and other widely used non-steroidal anti-inflammatory drugs inhibit antibody production in human cells. *Cell Immunol*. 2009;258(1):18-28.
12. Ryan EP, Pollock SJ, Murant TI, Bernstein SH, Felgar RE, Phipps RP. Activated human B lymphocytes express cyclooxygenase-2 and cyclooxygenase inhibitors attenuate antibody production. *J Immunol*. 2005;174(5):2619-2626.
13. Graham NM, Burrell CJ, Douglas RM, Debelle P, Davies L. Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function, viral shedding, and clinical status in rhinovirus-infected volunteers. *J Infect Dis*. 1990;162(6):1277-1282.
14. Shirey KA, Lai W, Pletneva LM, et al. Role of the lipoxygenase pathway in RSV-induced alternatively activated macrophages leading to resolution of lung pathology. *Mucosal Immunol*. 2014;7(3):549-557.
15. Tam VC, Quehenberger O, Oshansky CM, et al. Lipidomic profiling of influenza infection identifies mediators that induce and resolve inflammation. *Cell*. 2013;154(1):213-227.
16. Shirey KA, Pletneva LM, Puche AC, et al. Control of RSV-induced lung injury by alternatively activated macrophages is IL-4R alpha-, TLR4-, and IFN-beta-dependent. *Mucosal Immunol*. 2010;3(3):291-300.
17. Buckley CD, Gilroy DW, Serhan CN, Stockinger B, Tak PP. The resolution of inflammation. *Nat Rev Immunol*. 2013;13(1):59-66.
18. Coulombe F, Jaworska J, Verway M, et al. Targeted prostaglandin E2 inhibition enhances antiviral immunity through induction of type I interferon and apoptosis in macrophages. *Immunity*. 2014;40(4):554-568.
19. Tate MD, Ong JDH, Dowling JK, et al. Reassessing the role of the NLRP3 inflammasome during pathogenic influenza A virus infection via temporal inhibition. *Sci Rep*. 2016;6:27912.
20. Zhao J, Legge K, Perlman S. Age-related increases in PGD(2) expression impair respiratory DC migration, resulting in diminished T cell responses upon respiratory virus infection in mice. *J Clin Investig*. 2011;121(12):4921-4930.
21. Andreakos E, Papadaki M, Serhan CN. Dexamethasone, pro-resolving lipid mediators and resolution of inflammation in COVID-19. *Allergy*. 2021;76(3):626-628.
22. Moore N, Bosco-Levy P, Thurin N, Blin P, Droz-Perroteau C. NSAIDs and COVID-19: a systematic review and meta-analysis. *Drug Saf*. 2021;44(9):929-938.
23. Qiao W, Wang C, Chen B, et al. Ibuprofen attenuates cardiac fibrosis in streptozotocin-induced diabetic rats. *Cardiology*. 2015;131(2):97-106.
24. Miyoshi H, VanDussen KL, Malvin NP, et al. Prostaglandin E2 promotes intestinal repair through an adaptive cellular response of the epithelium. *Embo J*. 2017;36(1):5-24.
25. Alfajaro MM, Choi JS, Kim DS, et al. Activation of COX-2/PGE2 promotes sapovirus replication via the inhibition of nitric oxide production. *J Virol*. 2017;91(3).
26. Radzikowska U, Ding M, Tan G, et al. Distribution of ACE2, CD147, CD26, and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors. *Allergy*. 2020;75(11):2829-2845.
27. Zhao J, Zhao J, Legge K, Perlman S. Age-related increases in PGD(2) expression impair respiratory DC migration, resulting in diminished T cell responses upon respiratory virus infection in mice. *J Clin Investig*. 2011;121(12):4921-4930.
28. Theken KN, Tang SY, Sengupta S, FitzGerald GA. The roles of lipids in SARS-CoV-2 viral replication and the host immune response. *J Lipid Res*. 2021;62:100129.
29. Sokolowska M, Chen LY, Liu Y, et al. Prostaglandin E2 inhibits its NLRP3 inflammasome activation through EP4 receptor and intracellular Cyclic AMP in human macrophages. *J Immunol*. 2015;194(11):5472-5487.
30. Vijay R, Fehr AR, Janowski AM, et al. Virus-induced inflammasome activation is suppressed by prostaglandin D_2/DP1 signaling. *Proc Natl Acad Sci*. 2017;114(27):E5444-E5453.
31. Martha JW, Pranata R, Lim MA, Wibowo A, Akbar MR. Active prescription of low-dose aspirin during or prior to hospitalization and mortality in COVID-19: a systematic review and meta-analysis of adjusted effect estimates. *Int J Infect Dis*. 2021;108:6-12.

32. Sokolowska M, Lukasik ZM, Agache I, et al. Immunology of COVID-19: mechanisms, clinical outcome, diagnostics, and perspectives-a report of the European Academy of Allergy and Clinical Immunology (EAACI). *Allergy*. 2020;75(10):2445-2476.
33. Chen JS, Alfajaro MM, Chow RD, et al. Non-steroidal anti-inflammatory drugs dampen the cytokine and antibody response to SARS-CoV-2 infection. *J Virol*. 2021;95(7).
34. Archambault AS, Zaid Y, Rakotoarivelo V, et al. High levels of eicosanoids and docosanoids in the lungs of intubated COVID-19 patients. *Faseb J*. 2021;35(6):e21666.
35. Schwarz B, Sharma L, Roberts L, et al. Cutting edge: severe SARS-CoV-2 infection in humans is defined by a shift in the serum lipidome, resulting in dysregulation of eicosanoid immune mediators. *J Immunol*. 2021;206(2):329-334.
36. Buchheit KM, Hacker JJ, Gakpo DH, Mullur J, Sohail A, Laidlaw TM. Influence of daily aspirin therapy on ACE2 expression and function—implications for SARS-CoV-2 and patients with aspirin-exacerbated respiratory disease. *Clin Exp Allergy*. 2021;51(7):968-971.
37. Terrier O, Dilly S, Pizzorno A, et al. Antiviral properties of the NSAID drug naproxen targeting the nucleoprotein of SARS-CoV-2 coronavirus. *Molecules (Basel, Switzerland)*. 2021;26(9):2593.
38. Anderson BJ. Paracetamol (Acetaminophen): mechanisms of action. *Paediatr Anaesth*. 2008;18(10):915-921.
39. Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology*. 2013;21(3):201-232.
40. Reese JT, Coleman B, Chan L, et al. NSAID use and clinical outcomes in COVID-19 patients: A 38-center retrospective cohort study. *medRxiv*. 2021. doi:10.1101/2021.04.13.21255438
41. Rinott E, Kozer E, Shapira Y, Bar-Haim A, Youngster I. Ibuprofen use and clinical outcomes in COVID-19 patients. *Clin Microbiol Infect*. 2020;26(9):1259.e1255-1259.e1257.
42. Abu Esba LC, Alqahtani RA, Thomas A, Shamas N, Alswaidan L, Mardawi G. Ibuprofen and NSAID use in COVID-19 infected patients is not associated with worse outcomes: a prospective cohort study. *Infect Dis Ther*. 2021;10(1):253-268.
43. Drake TM, Fairfield CJ, Pius R, et al. Non-steroidal anti-inflammatory drug use and outcomes of COVID-19 in the ISARIC Clinical Characterisation Protocol UK cohort: a matched, prospective cohort study. *Lancet Rheumatol*. 2021;3(7):e498–e506. doi:10.1016/S2665-9913(21)00104-1
44. Park J, Lee SH, You SC, Kim J, Yang K. Non-steroidal anti-inflammatory agent use may not be associated with mortality of coronavirus disease 19. *Sci Rep*. 2021;11(1):5087.
45. Ricke-Hoch M, Stelling E, Lasswitz L, et al. Impaired immune response mediated by prostaglandin E2 promotes severe COVID-19 disease. *PLoS One*. 2021;16(8):e0255335.
46. Peters-Golden M, Henderson WR Jr. Leukotrienes. *N Engl J Med*. 2007;357(18):1841-1854.
47. Capra V, Thompson MD, Sala A, Cole DE, Folco G, Rovati GE. Cysteinyl-leukotrienes and their receptors in asthma and other inflammatory diseases: critical update and emerging trends. *Med Res Rev*. 2007;27(4):469-527.
48. Diamant Z, Mantzouranis E, Bjermer L. Montelukast in the treatment of asthma and beyond. *Expert Rev Clin Immunol*. 2009;5(6):639-658.
49. Langlois A, Ferland C, Tremblay GM, Laviolette M. Montelukast regulates eosinophil protease activity through a leukotriene-independent mechanism. *J Allergy Clin Immunol*. 2006;118(1):113-119.
50. Tahan F, Jazrawi E, Moodley T, Rovati GE, Adcock IM. Montelukast inhibits tumour necrosis factor-alpha-mediated interleukin-8 expression through inhibition of nuclear factor-kappaB p65-associated histone acetyltransferase activity. *Clin Exp Allergy*. 2008;38(5):805-811.
51. Mamedova L, Capra V, Accomazzo MR, et al. CysLT1 leukotriene receptor antagonists inhibit the effects of nucleotides acting at P2Y receptors. *Biochem Pharmacol*. 2005;71(1–2):115-125.
52. Woszczek G, Chen LY, Alsaaty S, Nagineni S, Shelhamer JH. Concentration-dependent noncysteinyl leukotriene type 1 receptor-mediated inhibitory activity of leukotriene receptor antagonists. *J Immunol*. 2010;184(4):2219-2225.
53. Ichiyama T, Hasegawa S, Umeda M, Terai K, Matsubara T, Furukawa S. Pranlukast inhibits NF-kappa B activation in human monocytes/macrophages and T cells. *Clin Exp Allergy*. 2003;33(6):802-807.
54. Ishinaga H, Takeuchi K, Kishioka C, Suzuki S, Basbaum C, Majima Y. Pranlukast inhibits NF-kappaB activation and MUC2 gene expression in cultured human epithelial cells. *Pharmacology*. 2005;73(2):89-96.
55. Ciana P, Fumagalli M, Trincavelli ML, et al. The orphan receptor GPR17 identified as a new dual uracil nucleotides/cysteinyl-leukotrienes receptor. *EMBO J*. 2006;25(19):4615-4627.
56. Ramires R, Caiaffa MF, Tursi A, Haeggstrom JZ, Macchia L. Novel inhibitory effect on 5-lipoxygenase activity by the anti-asthma drug montelukast. *Biochem Biophys Res Comm*. 2004;324(2):815-821.
57. Rius M, Hummel-Eisenbeiss J, Keppler D. ATP-dependent transport of leukotrienes B4 and C4 by the multidrug resistance protein ABCC4 (MRP4). *J Pharmacol Exp Ther*. 2008;324(1):86-94.
58. Ravasi S, Capra V, Panigalli T, Rovati GE, Nicosia S. Pharmacological differences among CysLT(1) receptor antagonists with respect to LTC(4) and LTD(4) in human lung parenchyma. *Biochem Pharmacol*. 2002;63(8):1537-1546.
59. Lynch KR, O'Neill GP, Liu Q, et al. Characterization of the human cysteinyl leukotriene $CysLT_1$ receptor. *Nature*. 1999;399:789-793.
60. Sarau HM, Ames RS, Chambers J, et al. Identification, molecular cloning, expression, and characterization of a cysteinyl leukotriene receptor. *Mol Pharmacol*. 1999;56(3):657-663.
61. Reiss TF, Altman LC, Chervinsky P, et al. Effects of montelukast (MK-0476), a new potent cysteinyl leukotriene (LTD4) receptor antagonist, in patients with chronic asthma. *J Allergy Clin Immunol*. 1996;98(3):528-534.
62. Altman LC, Munk Z, Seltzer J, et al. A placebo-controlled, dose-ranging study of montelukast, a cysteinyl leukotriene-receptor antagonist. Montelukast Asthma Study Group. *J Allergy Clin Immunol*. 1998;102(1):50-56.
63. Malmstrom K, Rodriguez-Gomez G, Guerra J, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. Montelukast/Beclomethasone Study Group. *Ann Intern Med*. 1999;130(6):487-495.
64. Lazarinis N, Bood J, Gomez C, et al. Leukotriene E4 induces airflow obstruction and mast cell activation through the cysteinyl leukotriene type 1 receptor. *J Allergy Clin Immunol*. 2018;142(4):1080-1089.
65. Drazen JM, Yandava CN, Dube L, et al. Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. *Nat Genet*. 1999;22(2):168-170.
66. Mougey EB, Feng H, Castro M, Irvin CG, Lima JJ. Absorption of montelukast is transporter mediated: a common variant of OATP2B1 is associated with reduced plasma concentrations and poor response. *Pharmacogenet Genomics*. 2009;19(2):129-138.
67. Scott JP, Peters-Golden M. Antileukotriene agents for the treatment of lung disease. *Am J Respir Crit Care Med*. 2013;188(5):538-544.
68. Kolmert J, Gomez C, Balgoma D, et al. Urinary leukotriene E4 and prostaglandin D2 metabolites increase in adult and childhood severe asthma characterized by type 2 inflammation. a clinical observational study. *Am J Respir Crit Care Med*. 2021;203(1):37-53.
69. Gaber F, Daham K, Higashi A, et al. Increased levels of cysteinyl-leukotrienes in saliva, induced sputum, urine and

blood from patients with aspirin-intolerant asthma. *Thorax*. 2008;63(12):1076-1082.
70. Rabinovitch N, Graber NJ, Chinchilli VM, et al. Urinary leukotriene E4/exhaled nitric oxide ratio and montelukast response in childhood asthma. *J Allergy Clin Immunol*. 2010;126(3):545-551.e4.
71. Rabinovitch N, Mauger DT, Reisdorph N, et al. Predictors of asthma control and lung function responsiveness to step 3 therapy in children with uncontrolled asthma. *J Allergy Clin Immunol*. 2014;133(2):350-356.
72. Edelman JM, Turpin JA, Bronsky EA, et al. Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction. A randomized, double-blind trial. Exercise Study Group. *Ann Intern Med*. 2000;132(2):97-104.
73. Price DB, Swern A, Tozzi CA, Philip G, Polos P. Effect of montelukast on lung function in asthma patients with allergic rhinitis: analysis from the COMPACT trial. *Allergy*. 2006;61(6):737-742.
74. Dahlen SE, Malmstrom K, Nizankowska E, et al. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med*. 2002;165(1):9-14.
75. Bisgaard H, Zielen S, Garcia-Garcia ML, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med*. 2005;171(4):315-322.
76. Bozek A, Warkocka-Szoltysek B, Filipowska-Gronska A, Jarzab J. Montelukast as an add-on therapy to inhaled corticosteroids in the treatment of severe asthma in elderly patients. *J Asthma*. 2012;49(5):530-534.
77. Price D, Musgrave SD, Shepstone L, et al. Leukotriene antagonists as first-line or add-on asthma-controller therapy. *N Engl J Med*. 2011;364(18):1695-1707.
78. Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax*. 2002;57(3):226-230.
79. Gaki E, Papatheodorou G, Ischaki E, Grammenou V, Papa I, Loukides S. Leukotriene E(4) in urine in patients with asthma and COPD–the effect of smoking habit. *Respir Med*. 2007;101(4):826-832.
80. Lazarus SC, Chinchilli VM, Rollings NJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med*. 2007;175(8):783-790.
81. Price D, Popov TA, Bjermer L, et al. Effect of montelukast for treatment of asthma in cigarette smokers. *J Allergy Clin Immunol*. 2013;131(3):763-771.
82. Giouleka P, Papatheodorou G, Lyberopoulos P, et al. Body mass index is associated with leukotriene inflammation in asthmatics. *Eur J Clin Invest*. 2011;41(1):30-38.
83. Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. *Eur Respir J*. 2006;27(3):495-503.
84. Kowalski ML, Makowska JS, Blanca M, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) - classification, diagnosis and management: review of the EAACI/ENDA(#) and GA2LEN/HANNA*. *Allergy*. 2011;66(7):818-829.
85. Pace S, Sautebin L, Werz O. Sex-biased eicosanoid biology: impact for sex differences in inflammation and consequences for pharmacotherapy. *Biochem Pharmacol*. 2017;145:1-11.
86. Pergola C, Dodt G, Rossi A, et al. ERK-mediated regulation of leukotriene biosynthesis by androgens: a molecular basis for gender differences in inflammation and asthma. *Proc Natl Acad Sci USA*. 2008;105(50):19881-19886.
87. Pace S, Pergola C, Dehm F, et al. Androgen-mediated sex bias impairs efficiency of leukotriene biosynthesis inhibitors in males. *J Clin Investig*. 2017;127(8):3167-3176.
88. Pergola C, Schaible AM, Nikels F, Dodt G, Northoff H, Werz O. Progesterone rapidly down-regulates the biosynthesis of 5-lipoxygenase products in human primary monocytes. *Pharmacol Res*. 2015;94:42-50.
89. Rossi A, Roviezzo F, Sorrentino R, et al. Leukotriene-mediated sex dimorphism in murine asthma-like features during allergen sensitization. *Pharmacol Res*. 2019;139:182-190.
90. Pace S, Werz O. Impact of androgens on inflammation-related lipid mediator biosynthesis in innate immune cells. *Front Immunol*. 2020;11:1356.
91. Esposito R, Spaziano G, Giannattasio D, et al. Montelukast improves symptoms and lung function in asthmatic women compared with men. *Front Pharmacol*. 2019;10:1094.
92. Rabinovitch N, Strand M, Stuhlman K, Gelfand EW. Exposure to tobacco smoke increases leukotriene E4-related albuterol usage and response to montelukast. *J Allergy Clin Immunol*. 2008;121(6):1365-1371.
93. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy*. 2020;75(7):1564-1581.
94. Gao YD, Ding M, Dong X, et al. Risk factors for severe and critically ill COVID-19 patients: a review. *Allergy*. 2021;76(2):428-455.
95. Sisakht M, Solhjoo A, Mahmoodzadeh A, Fathalipour M, Kabiri M, Sakhteman A. Potential inhibitors of the main protease of SARS-CoV-2 and modulators of arachidonic acid pathway: Non-steroidal anti-inflammatory drugs against COVID-19. *Comput Biol Med*. 2021;136: 104686.
96. Fidan C, Aydogdu A. As a potential treatment of COVID-19: montelukast. *Med Hypotheses*. 2020;142: 109828.
97. Aigner L, Pietrantonio F, Bessa de Sousa DM, et al. The leukotriene receptor antagonist montelukast as a potential COVID-19 therapeutic. *Front Mol Biosci*. 2020;7:610132.
98. Barré J, Sabatier JM, Annweiler C. Montelukast drug may improve COVID-19 prognosis: a review of evidence. *Front Pharmacol*. 2020;11:1344.
99. Crimi N, Mastruzzo C, Pagano C, Lisitano N, Palermo F, Vancheri C. Montelukast protects against bradykinin-induced bronchospasm. *J Allergy Clin Immunol*. 2005;115(4):870-872.
100. England JT, Abdulla A, Biggs CM, et al. Weathering the COVID-19 storm: lessons from hematologic cytokine syndromes. *Blood Rev*. 2021;45: 100707.
101. Fajgenbaum DC, June CH. Cytokine storm. *N Engl J Med*. 2020;383(23):2255-2273.
102. Sala A, Murphy RC, Voelkel NF. Direct airway injury results in elevated levels of sulfidopeptide leukotrienes, detectable in airway secretions. *Prostaglandins*. 1991;42(1):1-7.
103. Sanghai N, Tranmer GK. Taming the cytokine storm: repurposing montelukast for the attenuation and prophylaxis of severe COVID-19 symptoms. *Drug Discov Today*. 2020;25(12):2076-2079.
104. Maeba S, Ichiyama T, Ueno Y, Makata H, Matsubara T, Furukawa S. Effect of montelukast on nuclear factor kappaB activation and proinflammatory molecules. *Ann Allergy Asthma Immunol*. 2005;94(6):670-674.
105. Ueda T, Takeno S, Furukido K, Hirakawa K, Yajin K. Leukotriene receptor antagonist pranlukast suppresses eosinophil infiltration and cytokine production in human nasal mucosa of perennial allergic rhinitis. *Ann Otol Rhinol Laryngol*. 2003;112(11):955-961.
106. Almerie MQ, Kerrigan DD. The association between obesity and poor outcome after COVID-19 indicates a potential therapeutic role for montelukast. *Med Hypotheses*. 2020;143: 109883.
107. Khan AR, Misdary C, Yegya-Raman N, et al. Montelukast in hospitalized patients diagnosed with COVID-19. *J Asthma*. 2021;1-7.
108. Bozek A, Winterstein J. Montelukast's ability to fight COVID-19 infection. *J Asthma*. 2021;58(10):1348-1349.
109. Hoxha M, Tedesco CC, Quaglin S, et al. Montelukast use decreases cardiovascular events in asthmatics. *Front Pharmacol*. 2020;11:611561.
110. Funk CD. Leukotriene modifiers as potential therapeutics for cardiovascular disease. *Nat Rev Drug Discov*. 2005;4(8):664-672.

111. Camera M, Canzano P, Brambilla M, Rovati GE. Montelukast inhibits platelet activation induced by plasma from COVID-19 patients. *Front Pharmacol*. 2022;13.
112. Funk CD, Ardakani A. A novel strategy to mitigate the hyperinflammatory response to COVID-19 by targeting leukotrienes. *Front Pharmacol*. 2020;11:1214.
113. Pettipher R, Hansel TT, Armer R. Antagonism of the prostaglandin D2 receptors DP1 and CRTH2 as an approach to treat allergic diseases. *Nat Rev Drug Discov*. 2007;6(4):313-325.
114. Claar D, Hartert TV, Peebles RS Jr. The role of prostaglandins in allergic lung inflammation and asthma. *Expert Rev Respir Med*. 2015;9(1):55-72.
115. Boonpiyathad T, Capova G, Duchna HW, et al. Impact of high-altitude therapy on type-2 immune responses in asthma patients. *Allergy*. 2020;75(1):84-94.
116. Rudulier CD, Tonti E, James E, Kwok WW, Larché M. Modulation of CRTh2 expression on allergen-specific T cells following peptide immunotherapy. *Allergy*. 2019;74(11):2157-2166.
117. Diamant Z, Aalders W, Parulekar A, Bjermer L, Hanania NA. Targeting lipid mediators in asthma: time for reappraisal. *Curr Opin Pulm Med*. 2019;25(1):121-127.
118. Brightling CE, Brusselle G, Altman P. The impact of the prostaglandin D(2) receptor 2 and its downstream effects on the pathophysiology of asthma. *Allergy*. 2020;75(4):761-768.
119. Singh D, Cadden P, Hunter M, et al. Inhibition of the asthmatic allergen challenge response by the CRTH2 antagonist OC000459. *Eur Respir J*. 2013;41(1):46-52.
120. Diamant Z, Sidharta PN, Singh D, et al. Setipiprant, a selective CRTH2 antagonist, reduces allergen-induced airway responses in allergic asthmatics. *Clin Exp Allergy*. 2014;44(8):1044-1052.
121. Xia J, Abdu S, Maguire TJA, Hopkins C, Till SJ, Woszczek G. Prostaglandin D(2) receptors in human mast cells. *Allergy*. 2020;75(6):1477-1480.
122. Beasley R, Varley J, Robinson C, Holgate ST. Cholinergic-mediated bronchoconstriction induced by prostaglandin D2, its initial metabolite 9 alpha,11 beta-PGF2, and PGF2 alpha in asthma. *Am Rev Respir Dis*. 1987;136(5):1140-1144.
123. Diamant Z, Timmers MC, van der Veen H, et al. The effect of MK-0591, a novel 5-lipoxygenase activating protein inhibitor, on leukotriene biosynthesis and allergen-induced airway responses in asthmatic subjects in vivo. *J Allergy Clin Immunol*. 1995;95(1 Pt 1):42-51.
124. Pettipher R, Hunter MG, Perkins CM, et al. Heightened response of eosinophilic asthmatic patients to the CRTH2 antagonist OC000459. *Allergy*. 2014;69(9):1223-1232.
125. Ratner P, Andrews CP, Hampel FC, et al. Efficacy and safety of setipiprant in seasonal allergic rhinitis: results from Phase 2 and Phase 3 randomized, double-blind, placebo- and active-referenced studies. *Allergy Asthma Clin Immunol*. 2017;13:18.
126. Saunders R, Kaul H, Berair R, et al. DP2 antagonism reduces airway smooth muscle mass in asthma by decreasing eosinophilia and myofibroblast recruitment. *Sci Transl Med*. 2019;11(479).
127. Fajt ML, Gelhaus SL, Freeman B, et al. Prostaglandin D(2) pathway upregulation: relation to asthma severity, control, and TH2 inflammation. *J Allergy Clin Immunol*. 2013;131(6):1504-1512.
128. Brightling CE, Brusselle G, Altman P. The impact of the prostaglandin D2 receptor 2 and its downstream effects on the pathophysiology of asthma. *Allergy*. 2020;75(4):761-768.
129. Shiraishi Y, Asano K, Niimi K, et al. Cyclooxygenase-2/prostaglandin D2/CRTH2 pathway mediates double-stranded RNA-induced enhancement of allergic airway inflammation. *J Immunol*. 2008;180(1):541-549.
130. Werder RB, Lynch JP, Simpson JC, et al. PGD2/DP2 receptor activation promotes severe viral bronchiolitis by suppressing IFN-lambda production. *Sci Transl Med*. 2018;10(440).
131. Gupta A, Chander CK. Prostaglandin D2 as a mediator of lymphopenia and a therapeutic target in COVID-19 disease. *Med Hypotheses*. 2020;143: 110122.
132. Safholm J, Manson ML, Bood J, et al. Prostaglandin E2 inhibits mast cell-dependent bronchoconstriction in human small airways through the E prostanoid subtype 2 receptor. *J Allergy Clin Immunol*. 2015;136(5):1232-1239.e1231.
133. Lu HC, Mackie K. An introduction to the endogenous cannabinoid system. *Biol Psychiatry*. 2016;79(7):516-525.
134. Di Marzo V. New approaches and challenges to targeting the endocannabinoid system. *Nat Rev Drug Discov*. 2018;17(9):623-639.
135. Velasco G, Sanchez C, Guzman M. Towards the use of cannabinoids as antitumour agents. *Nat Rev Cancer*. 2012;12(6):436-444.
136. Turcotte C, Chouinard F, Lefebvre JS, Flamand N. Regulation of inflammation by cannabinoids, the endocannabinoids 2-arachidonoyl-glycerol and arachidonoyl-ethanolamide, and their metabolites. *J Leukoc Biol*. 2015;97(6):1049-1070.
137. Deng H, Li W. Monoacylglycerol lipase inhibitors: modulators for lipid metabolism in cancer malignancy, neurological and metabolic disorders. *Acta Pharm Sin B*. 2020;10(4):582-602.
138. Celorrio M, Fernandez-Suarez D, Rojo-Bustamante E, et al. Fatty acid amide hydrolase inhibition for the symptomatic relief of Parkinson's disease. *Brain Behav Immun*. 2016;57:94-105.
139. Alhouayek M, Muccioli GG. COX-2-derived endocannabinoid metabolites as novel inflammatory mediators. *Trends Pharmacol Sci*. 2014;35(6):284-292.
140. Fowler CJ. NSAIDs: eNdocannabinoid stimulating anti-inflammatory drugs? *Trends Pharmacol Sci*. 2012;33(9):468-473.
141. Angelina A, Perez-Diego M, Lopez-Abente J, Palomares O. The role of cannabinoids in allergic diseases: Collegium Internationale Allergologicum (CIA) update 2020. *Int Arch Allergy Immunol*. 2020;181(8):565-584.
142. Sugawara K, Zakany N, Hundt T, et al. Cannabinoid receptor 1 controls human mucosal-type mast cell degranulation and maturation in situ. *J Allergy Clin Immunol*. 2013;132(1):182-193.
143. Sugawara K, Biro T, Tsuruta D, et al. Endocannabinoids limit excessive mast cell maturation and activation in human skin. *J Allergy Clin Immunol*. 2012;129(3):726-738.e728.
144. Braun A, Engel T, Aguilar-Pimentel JA, et al. Beneficial effects of cannabinoids (CB) in a murine model of allergen-induced airway inflammation: role of CB1/CB2 receptors. *Immunobiology*. 2011;216(4):466-476.
145. Vuolo F, Abreu SC, Michels M, et al. Cannabidiol reduces airway inflammation and fibrosis in experimental allergic asthma. *Eur J Pharmacol*. 2019;843:251-259.
146. Jan TR, Farraj AK, Harkema JR, Kaminski NE. Attenuation of the ovalbumin-induced allergic airway response by cannabinoid treatment in A/J mice. *Toxicol Appl Pharmacol*. 2003;188(1):24-35.
147. Giannini L, Nistri S, Mastroianni R, et al. Activation of cannabinoid receptors prevents antigen-induced asthma-like reaction in guinea pigs. *J Cell Mol Med*. 2008;12(6A):2381-2394.
148. Gaffal E, Glodde N, Jakobs M, Bald T, Tuting T. Cannabinoid 1 receptors in keratinocytes attenuate fluorescein isothiocyanate-induced mouse atopic-like dermatitis. *Exp Dermatol*. 2014;23(6):401-406.
149. Kim HJ, Kim B, Park BM, et al. Topical cannabinoid receptor 1 agonist attenuates the cutaneous inflammatory responses in oxazolone-induced atopic dermatitis model. *Int J Dermatol*. 2015;54(10):e401-408.
150. Nam G, Jeong SK, Park BM, et al. Selective cannabinoid receptor-1 agonists regulate mast cell activation in an oxazolone-induced atopic dermatitis model. *Ann Dermatol*. 2016;28(1):22-29.
151. Petrosino S, Verde R, Vaia M, Allara M, Iuvone T, Di Marzo V. Anti-inflammatory properties of cannabidiol, a nonpsychotropic cannabinoid, in experimental allergic contact dermatitis. *J Pharmacol Exp Ther*. 2018;365(3):652-663.

152. Vaia M, Petrosino S, De Filippis D, et al. Palmitoylethanolamide reduces inflammation and itch in a mouse model of contact allergic dermatitis. *Eur J Pharmacol*. 2016;791:669-674.
153. Petrosino S, Cristino L, Karsak M, et al. Protective role of palmitoylethanolamide in contact allergic dermatitis. *Allergy*. 2010;65(6):698-711.
154. Bozkurt TE, Kaya Y, Durlu-Kandilci NT, Onder S, Sahin-Erdemli I. The effect of cannabinoids on dinitrofluorobenzene-induced experimental asthma in mice. *Respir Physiol Neurobiol*. 2016;231:7-13.
155. Angelina A, Martin-Fontecha M, Ruckert B, et al. The cannabinoid WIN55212-2 restores rhinovirus-induced epithelial barrier disruption. *Allergy*. 2021;76(6):1900-1902.
156. Angelina A, Pérez-Diego M, López-Abente J, et al. Cannabinoids induce functional Tregs by promoting tolerogenic DCs via autophagy and metabolic reprograming. *Mucosal Immunol*. 2022;15(1):96-108.
157. Esposito G, Pesce M, Seguella L, et al. The potential of cannabidiol in the COVID-19 pandemic. *Br J Pharmacol*. 2020;177(21):4967-4970.
158. Tahamtan A, Tavakoli-Yaraki M, Salimi V. Opioids/cannabinoids as a potential therapeutic approach in COVID-19 patients. *Expert Rev Respir Med*. 2020;14(10):965-967.
159. Rossi F, Tortora C, Argenziano M, Di Paola A, Punzo F. Cannabinoid receptor type 2: a possible target in SARS-CoV-2 (CoV-19) infection? *Int J Mol Sci*. 2020;21(11):3809.
160. Frei RB, Luschnig P, Parzmair GP, et al. Cannabinoid receptor 2 augments eosinophil responsiveness and aggravates allergen-induced pulmonary inflammation in mice. *Allergy*. 2016;71(7):944-956.
161. Mimura T, Ueda Y, Watanabe Y, Sugiura T. The cannabinoid receptor-2 is involved in allergic inflammation. *Life Sci*. 2012;90(21–22):862-866.
162. Ferrini ME, Hong S, Stierle A, et al. CB2 receptors regulate natural killer cells that limit allergic airway inflammation in a murine model of asthma. *Allergy*. 2017;72(6):937-947.
163. Martin-Fontecha M, Eiwegger T, Jartti T, et al. The expression of cannabinoid receptor 1 is significantly increased in atopic patients. *J Allergy Clin Immunol*. 2014;133(3):926-929.e922.
164. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet (London, England)*. 2019;394(10209):1638-1650.
165. Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol*. 2020;146(3):595-605.
166. Dunican EM, Fahy JV. The role of type 2 inflammation in the pathogenesis of asthma exacerbations. *Ann Am Thorac Soc*. 2015;12(Suppl 2):S144-S149.
167. Bachert C, Zhang N, Cavaliere C, Weiping W, Gevaert E, Krysko O. Biologics for chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol*. 2020;145(3):725-739.
168. Bourdin A, Bjermer L, Brightling C, et al. ERS/EAACI statement on severe exacerbations in asthma in adults: facts, priorities and key research questions. *Eur Respir J*. 2019;54(3).
169. Del Giacco SR, Bakirtas A, Bel E, et al. Allergy in severe asthma. *Allergy*. 2017;72(2):207-220.
170. Dougherty RH, Fahy JV. Acute exacerbations of asthma: epidemiology, biology and the exacerbation-prone phenotype. *Clin Exp Allergy*. 2009;39(2):193-202.
171. Calhoun WJ, Dick EC, Schwartz LB, Busse WW. A common cold virus, rhinovirus 16, potentiates airway inflammation after segmental antigen bronchoprovocation in allergic subjects. *J Clin Investig*. 1994;94(6):2200-2208.
172. Peters-Golden M. Expanding roles for leukotrienes in airway inflammation. *Curr Allergy Asthma Rep*. 2008;8(4):367-373.
173. Diamant Z, Hiltermann JT, van Rensen EL, et al. The effect of inhaled leukotriene D4 and methacholine on sputum cell differentials in asthma. *Am J Respir Crit Care Med*. 1997;155(4):1247-1253.
174. Serrano-Candelas E, Martinez-Aranguren R, Valero A, et al. Comparable actions of omalizumab on mast cells and basophils. *Clin Exp Allergy*. 2016;46(1):92-102.
175. Zhang HP, Jia CE, Lv Y, Gibson PG, Wang G. Montelukast for prevention and treatment of asthma exacerbations in adults: Systematic review and meta-analysis. *Allergy Asthma Proc*. 2014;35(4):278-287.
176. Yang J, Luo J, Yang L, et al. Efficacy and safety of antagonists for chemoattractant receptor-homologous molecule expressed on Th2 cells in adult patients with asthma: a meta-analysis and systematic review. *Respir Res*. 2018;19(1):217.
177. Fitzgerald DA, Mellis CM. Leukotriene receptor antagonists in virus-induced wheezing : evidence to date. *Treat Respir Med*. 2006;5(6):407-417.
178. Laidlaw TM, Mullol J, Woessner KM, Amin N, Mannent LP. Chronic rhinosinusitis with nasal polyps and asthma. *J Allergy Clin Immunol Pract*. 2021;9(3):1133-1141.
179. Kowalski ML, Agache I, Bavbek S, et al. Diagnosis and management of NSAID-exacerbated respiratory disease (N-ERD)-a EAACI position paper. *Allergy*. 2019;74(1):28-39.
180. Celejewska-Wójcik N, Wójcik K, Ignacak-Popiel M, et al. Subphenotypes of nonsteroidal antiinflammatory disease-exacerbated respiratory disease identified by latent class analysis. *Allergy*. 2020;75(4):831-840.
181. Christie PE, Tagari P, Ford-Hutchinson AW, et al. Urinary leukotriene E4 concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. *Am Rev Respir Dis*. 1991;143(5 Pt 1):1025-1029.
182. Arm JP, O'Hickey SP, Spur BW, Lee TH. Airway responsiveness to histamine and leukotriene E4 in subjects with aspirin-induced asthma. *Am Rev Respir Dis*. 1989;140(1):148-153.
183. Cowburn AS, Sladek K, Soja J, et al. Overexpression of leukotriene C4 synthase in bronchial biopsies from patients with aspirin-intolerant asthma. *J Clin Investig*. 1998;101(4):834-846.
184. Corrigan CJ, Napoli RL, Meng Q, et al. Reduced expression of the prostaglandin E2 receptor E-prostanoid 2 on bronchial mucosal leukocytes in patients with aspirin-sensitive asthma. *J Allergy Clin Immunol*. 2012;129(6):1636-1646.
185. Szczeklik A, Mastalerz L, Nizankowska E, Cmiel A. Protective and bronchodilator effects of prostaglandin E and salbutamol in aspirin-induced asthma. *Am J Respir Crit Care Med*. 1996;153(2):567-571.
186. Yamaguchi H, Higashi N, Mita H, et al. Urinary concentrations of 15-epimer of lipoxin A(4) are lower in patients with aspirin-intolerant compared with aspirin-tolerant asthma. *Clin Exp Allergy*. 2011;41(12):1711-1718.
187. Cahill KN, Bensko JC, Boyce JA, Laidlaw TM. Prostaglandin D_2: a dominant mediator of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2015;135(1):245-252.
188. Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy*. 2013;68(10):1219-1232.
189. Flower RJ. The development of COX2 inhibitors. *Nat Rev Drug Discov*. 2003;2(3):179-191.
190. Doña I, Barrionuevo E, Salas M, et al. NSAIDs-hypersensitivity often induces a blended reaction pattern involving multiple organs. *Sci Rep*. 2018;8(1):16710.
191. FitzGerald GA. COX-2 and beyond: approaches to prostaglandin inhibition in human disease. *Nat Rev Drug Discov*. 2003;2(11):879-890.
192. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather

than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci USA*. 1999;96(13):7563-7568.
193. Dona I, Perez-Sanchez N, Eguiluz-Gracia I, et al. Progress in understanding hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. *Allergy*. 2020;75(3):561-575.
194. Eguiluz-Gracia I, Tay TR, Hew M, et al. Recent developments and highlights in biomarkers in allergic diseases and asthma. *Allergy*. 2018;73(12):2290-2305.
195. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. *BMJ*. 1975;1(5949):67-69.
196. Zembowicz A, Mastalerz L, Setkowicz M, Radziszewski W, Szczeklik A. Safety of cyclooxygenase 2 inhibitors and increased leukotriene synthesis in chronic idiopathic urticaria with sensitivity to nonsteroidal anti-inflammatory drugs. *Arch Dermatol*. 2003;139(12):1577-1582.
197. Setkowicz M, Mastalerz L, Podolec-Rubis M, Sanak M, Szczeklik A. Clinical course and urinary eicosanoids in patients with aspirin-induced urticaria followed up for 4 years. *J Allergy Clin Immunol*. 2009;123(1):174-178.
198. Di Lorenzo G, Pacor ML, Candore G, et al. Polymorphisms of cyclo-oxygenases and 5-lipo-oxygenase-activating protein are associated with chronic spontaneous urticaria and urinary leukotriene E4. *Eur J Dermatol*. 2011;21(1):47-52.
199. Doña I, Jurado-Escobar R, Perkins JR, et al. Eicosanoid mediator profiles in different phenotypes of nonsteroidal anti-inflammatory drug-induced urticaria. *Allergy*. 2019;74(6):1135-1144.
200. Di Lorenzo G, Pacor ML, Vignola AM, et al. Urinary metabolites of histamine and leukotrienes before and after placebo-controlled challenge with ASA and food additives in chronic urticaria patients. *Allergy*. 2002;57(12):1180-1186.
201. Mastalerz L, Setkowicz M, Sanak M, Szczeklik A. Hypersensitivity to aspirin: common eicosanoid alterations in urticaria and asthma. *J Allergy Clin Immunol*. 2004;113(4):771-775.
202. Bohm I, Speck U, Schild H. A possible role for cysteinyl-leukotrienes in non-ionic contrast media induced adverse reactions. *Eur J Radiol*. 2005;55(3):431-436.
203. Stellato C, de Crescenzo G, Patella V, Mastronardi P, Mazzarella B, Marone G. Human basophil/mast cell releasability. XI. Heterogeneity of the effects of contrast media on mediator release. *J Allergy Clin Immunol*. 1996;97(3):838-850.
204. Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. *Am J Med*. 1998;104(5):413-421.
205. Waterbury LD, Silliman D, Jolas T. Comparison of cyclooxygenase inhibitory activity and ocular anti-inflammatory effects of ketorolac tromethamine and bromfenac sodium. *Curr Med Res Opin*. 2006;22(6):1133-1140.
206. Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc Natl Acad Sci USA*. 1993;90(24):11693-11697.
207. Campos C, de Gregorio R, García-Nieto R, Gago F, Ortiz P, Alemany S. Regulation of cyclooxygenase activity by metamizol. *Eur J Pharmacol*. 1999;378(3):339-347.
208. Israel E, Cohn J, Dubé L, Drazen JM. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. A randomized controlled trial. Zileuton Clinical Trial Group. *JAMA*. 1996;275(12):931-936.
209. Castro M, Kerwin E, Miller D, et al. Efficacy and safety of fevipiprant in patients with uncontrolled asthma: Two replicate, phase 3, randomised, double-blind, placebo-controlled trials (ZEAL-1 and ZEAL-2). *EClinicalMedicine*. 2021;35: 100847.
210. Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371(3):203-212.

How to cite this article: Sokolowska M, Rovati GE, Diamant Z, et al. Effects of non-steroidal anti-inflammatory drugs and other eicosanoid pathway modifiers on antiviral and allergic responses: EAACI task force on eicosanoids consensus report in times of COVID-19. *Allergy*. 2022;00:1–18. doi:10.1111/all.15258