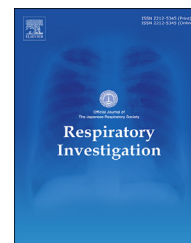


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Review

Anti-inflammatory effects of medications used for viral infection-induced respiratory diseases



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ABSTRACT

Respiratory viruses like rhinovirus, influenza virus, respiratory syncytial virus, and coronavirus cause several respiratory diseases, such as bronchitis, pneumonia, pulmonary fibrosis, and coronavirus disease 2019, and exacerbate bronchial asthma, chronic obstructive pulmonary disease, bronchiectasis, and diffuse panbronchiolitis. The production of inflammatory mediators and mucin and the accumulation of inflammatory cells have been reported in patients with viral infection-induced respiratory diseases. Interleukin (IL)-1 β , IL-6, IL-8, tumor necrosis factor- α , granulocyte-macrophage colony-stimulating factor, and regulated on activation normal T-cell expressed and secreted are

Abbreviations: A549, human type II lung cell line; AP-1, activator protein-1; ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; BEAS-2B, human bronchial epithelial cell line; Caco 2, human colon epithelial cancer cell line; ChAT, choline acetyl transferase; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CSF, colony-stimulating factor; CXCL10, CXC motif chemokine 10; DPB, diffuse panbronchiolitis; ECP, eosinophil cationic protein; FGF, fibroblast growth factor; GM, granulocyte-macrophage; HCoV, human coronavirus; HCT-8 cells, human colon adenocarcinoma cells; Hep-2, human epithelial type 2 cell line; HNE cells, human nasal epithelial cells; HTE cells, human tracheal epithelial cells; ICS, inhaled corticosteroid; ICU, intensive care unit; IFN, interferon; IL, interleukin; IP-10, interferon gamma inducible protein-10; IRF, interferon regulatory factor; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein-1; MERS, Middle East respiratory syndrome; MMP-9, matrix metalloproteinase-9; MRC-5, human fetal lung fibroblasts; NAC, N-acetylcysteine; NADPH, nicotinamide adenosine dinucleotide phosphate; NANS, sialic acid synthase; NCL-H292 cells, human pulmonary mucoepidermoid carcinoma cells; NF- κ B, nuclear factor kappa B; NO, nitric oxide; QOL, quality of life; RANTES, normal T-cell expressed and secreted; ROS, reactive oxygen species; RS virus, respiratory syncytial virus; RV, rhinovirus; SABA, short-acting β_2 -agonist; SARS, severe acute respiratory syndrome; sIL-2R, soluble IL-2 receptor; SPDEF, SAM-pointed domain-containing Ets-like factor; SpO₂, arterial blood oxygen saturation; TGF, transforming growth factor; THP-1, human monocytic leukemia cell line; TLR, toll-like receptor; TNF, tumor necrosis factor; URTI, upper respiratory tract infection; VEGF, vascular endothelial growth factor; Vero cells, African green monkey kidney epithelial cells.

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produced in the cells, including human airway and alveolar epithelial cells, partly through the activation of toll-like receptors, nuclear factor kappa B and p44/42 mitogen-activated protein kinase. These mediators are associated with the development of viral infection-induced respiratory diseases through the induction of inflammation and injury in the airway and lung, airway remodeling and hyperresponsiveness, and mucus secretion. Medications used to treat respiratory diseases, including corticosteroids, long-acting β_2 -agonists, long-acting muscarinic antagonists, mucolytic agents, antiviral drugs for severe acute respiratory syndrome coronavirus 2 and influenza virus, macrolides, and kampo medicines, reduce the production of viral infection-induced mediators, including cytokines and mucin, as determined in clinical, *in vivo*, or *in vitro* studies. These results suggest that the anti-inflammatory effects of these medications on viral infection-induced respiratory diseases may be associated with clinical benefits, such as improvements in symptoms, quality of life, and mortality rate, and can prevent hospitalization and the exacerbation of chronic obstructive pulmonary disease, bronchial asthma, bronchiectasis, and diffuse panbronchiolitis.

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1. Introduction

Respiratory viruses, including rhinovirus (RV), influenza virus, respiratory syncytial (RS) virus, seasonal human coronavirus (HCoV), and severe acute respiratory syndrome (SARS)-CoV-2, lead to the development of several respiratory diseases, such as bronchitis, pneumonia, pulmonary fibrosis, and coronavirus disease 2019 (COVID-19) [1–14], and exacerbate bronchial asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, interstitial pneumonia, and diffuse pan-bronchiolitis (DPB) [15–26] through airway and lung inflammation, fibrosis, cell damage, mucus secretion, airway hyperresponsiveness, and secondary bacterial infection [2,3,27–32] (Fig. 1).

Inhaled corticosteroids (ICSs), long-acting β_2 -agonists (LABAs), long-acting muscarinic antagonists (LAMAs), and mucolytic agents have anti-inflammatory and immunomodulatory effects [33–38] and have been used to improve symptoms, lung function, and quality of life (QOL) and prevent the viral-infection-induced exacerbation of bronchial asthma and COPD [39–46]. Furthermore, anti-influenza drugs, including neuraminidase inhibitors, and anti-SARS-CoV-2 drugs, including molnupiravir and interleukin (IL)-6 receptor antibodies, reduce virus infection-induced cytotoxicity and the production of proinflammatory cytokines [27,47–49]. Furthermore, treatment with macrolides, such as erythromycin, clarithromycin, roxithromycin, and azithromycin, improves symptoms and respiratory function, prevents the exacerbation of pulmonary diseases, including DPB, cystic fibrosis, bronchiectasis, COPD, and chronic rhinosinusitis, and increases the survival rate of patients with DPB [50–52]. Treatment with the Kampo medicine hochu-ekki-to also reduces the frequency of the common cold and exacerbations in patients with COPD [53].

Here, we report the anti-inflammatory effects of medications used to treat viral infection-induced respiratory diseases, including pneumonia, bronchitis, and bronchiolitis, as well as the exacerbation of COPD, bronchial asthma, bronchiectasis, and DPB.

2. Viral infection-induced respiratory diseases and inflammation

2.1. Viral infection-induced respiratory diseases

The outbreak of the COVID-19 pandemic due to the SARS-CoV-2 infection has continued for more than two years, and many patients have died from severe pneumonia [14]. The SARS-CoV-2 infection causes upper respiratory tract infection (URTI), pneumonia [14], the exacerbation of bronchiectasis [24], acute respiratory distress syndrome (ARDS), and pulmonary fibrosis [54] (Fig. 1). Furthermore, seasonal coronaviruses, including HCoV-229E, HCoV-HKU1, HCoV-NL63, and HCoV-OC43, induce URTI, bronchitis, the exacerbation of bronchial asthma and bronchiectasis, and pneumonia [6,7,15,23].

Influenza virus infection also induces URTI, bronchitis, bronchial asthma, the exacerbation of COPD, bronchiectasis and interstitial lung disease, viral and secondary bacterial pneumonia, and ARDS [1–4,6,10,15,22,23,25,55].

RVs are the major cause of common colds and the most frequent viruses detected throughout the year [56,57] and these viruses can induce bronchiolitis, pneumonia, the exacerbation of bronchial asthma, COPD, DPB, and asbestosis, and the development of pneumonia [5,8,9,15–23,26,55].

RS virus is also an important pathogen associated with the common cold and is the major cause of viral lower respiratory tract disease in infants and young children [11,58]. A relationship was reported between wheezing-associated respiratory illnesses and RS virus outbreaks in children [12]. RS virus infection was also demonstrated to be an important illness in elderly and high-risk adults [13,59] and was associated with the exacerbation of bronchial asthma, COPD, and interstitial lung disease in adults [15,22,25,60,61].

2.2. Viral-infection-induced airway and lung inflammations

2.2.1. SARS-CoV-2, SARS-CoV and seasonal coronaviruses
High levels of serum IL-6, soluble IL-2 receptor (sIL-2R), and C-reactive protein (CRP) were associated with disease severity in patients infected with SARS-CoV-2 [62,63]. *In vitro*, SARS-CoV infection induced the production of normal T-cell expressed and secreted (RANTES) in the human monocytic leukemia cell line THP-1 [64] and caused the production of higher quantities of IL-6 than infection with seasonal influenza virus in human airway epithelial cells [65]. Furthermore, the seasonal HCoV-229E induces the production of proinflammatory cytokines, including IL-1 β , IL-6, and IL-8, in human tracheal epithelial cells (HTE cells) and human nasal epithelial cells (HNE cells) by activating nuclear factor kappa B (NF- κ B) [36] (Fig. 1).

2.2.2. Influenza virus

The levels of IL-6 and interferon (IFN)- α in nasal lavage fluid and IL-6, IL-8, and tumor necrosis factor (TNF)- α in plasma were increased in an experimental influenza virus infection [10] (Fig. 1). Furthermore, sputum and serum levels of IL-8 and TNF- α and serum IL-6 levels were elevated during an influenza virus infection-induced COPD exacerbation [66,67].

Influenza virus infection induces production of the proinflammatory cytokines such as IL-1 β , IL-6, IL-8, and TNF- α [27,68,69] in airway epithelial cells and IL-6, IL-8, CXCL10 chemokine 10 (CXCL10, also known as IFN-gamma inducible protein-10, (IP-10)) and RANTES in human bronchial epithelial cells and A549 cells, which is a human type II lung cell line [70,71], by activating NF- κ B and mitogen-activated protein kinase (MAPK) p38 [71,72]. The 2009 pandemic influenza virus infection induced the detachment of epithelial cells, and the number of detached cells and lactate dehydrogenase (LDH) levels were related to viral titers, IL-6 levels, and NF- κ B activation [27].

Furthermore, influenza virus infection increased monocyte migration toward the supernatants of virus-infected A549 cells [71], induced lung fibrosis in mice via transforming growth factor (TGF)- β production [73], and stimulated human nasal mucosal progenitor cells to promote the recruitment and maturation of dendritic cells, which play an important role in the innate immune response [74].

In addition to the release of cytokines, reactive oxygen species (ROS) and nitrogen species are also released during influenza virus infection through mechanisms such as the

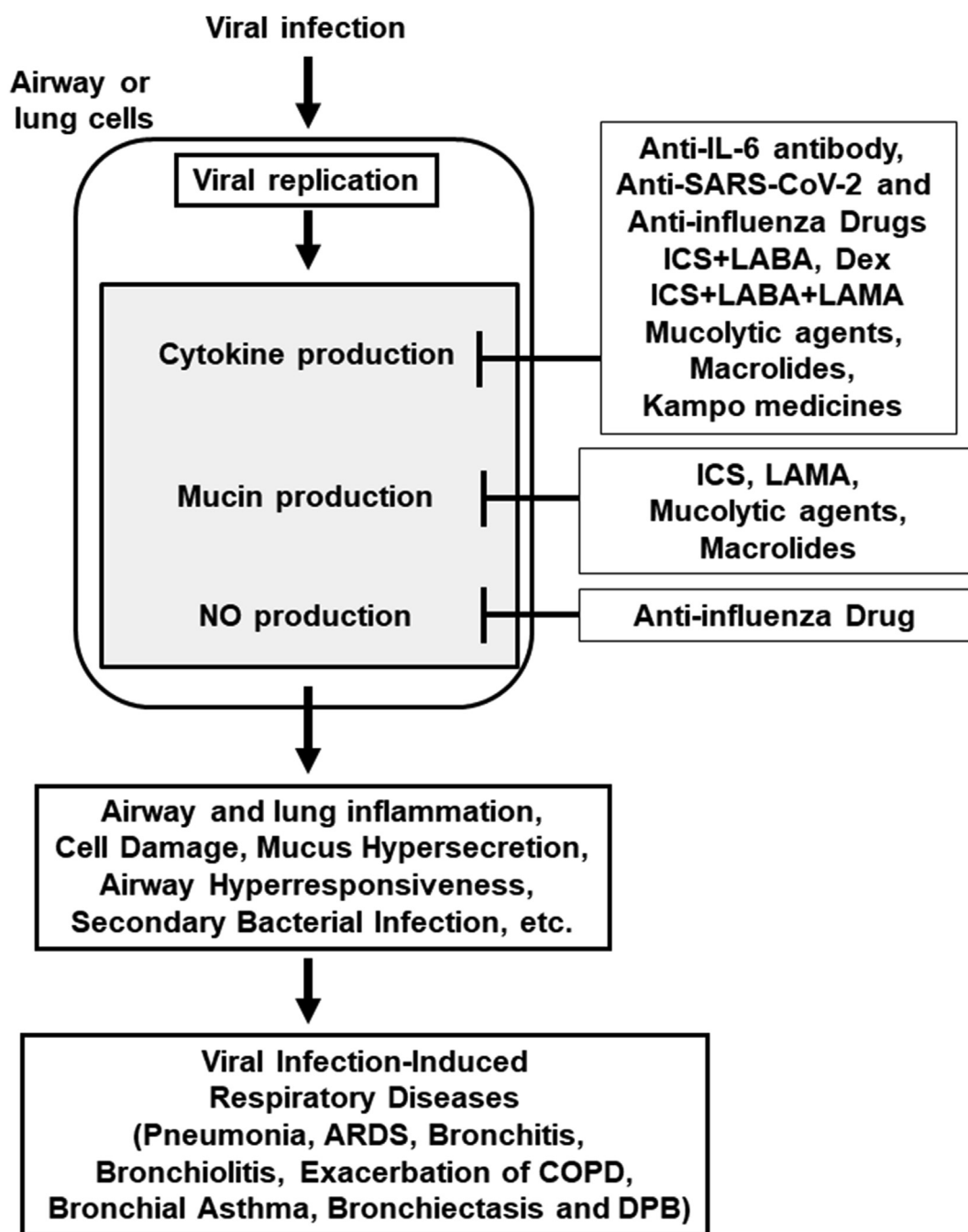


Fig. 1 – Mechanisms of viral infection-induced respiratory diseases and the sites at which medications act to treat these diseases. Medications, such as corticosteroids, LABA, LAMA, mucolytic agents, macrolides, anti-IL-6 antibodies, anti-SARS-CoV-2 and anti-influenza viral drugs, macrolides, and Kampo medicines may modulate the production of inflammatory mediators, such as cytokines, mucin and NO, and viral replication-induced cytotoxicity. Anti-IL-6 antibody, monoclonal IL-6 receptor blocking antibody; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; Dex, dexamethasone; DPB, diffuse panbronchiolitis; ICS, inhaled corticosteroid; IL, interleukin; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; NO, nitric oxide; SARS, severe acute respiratory syndrome.

activation of nicotinamide adenosine dinucleotide phosphate (NADPH) oxidase [75–77].

2.2.3. Rhinovirus

RV infection-induced cytokines, such as IL-5, IL-13, IL-25, and IL-33, were associated with persistent and severe

asthma [78], and the serum levels of eosinophil cationic protein (ECP), IL-5, IL-6, and IP-10 were elevated in RV-infected children with wheezing [79,80]. Furthermore, sputum IL-1 β , IL-5, IL-13, IL-25, and IL-33 levels, serum IL-6, IL-8, TNF- α , and IP-10 levels, plasma fibrinogen levels and the number of peripheral blood eosinophils were elevated

in patients with RV infection-exacerbated COPD [19,20,67,81].

RV infection induces the production of proinflammatory mediators, including IL-1 β , IL-6, IL-8, RANTES, IP-10, and granulocyte-macrophage (GM) colony-stimulating factor (CSF), in the human bronchial epithelial cell line BEAS-2B, primary HTE cells, human bronchial cells, HNE cells, and human tracheal submucosal gland cells [28,29,34,70,82–85] by activating NF- κ B [29] and toll-like receptor (TLR) [86,87]. RV infection induces the production of mucin (MUC5AC) in the cells of the human airway, bronchial epithelium, and tracheal submucosal gland [30,88,89] (Fig. 1), partly by activating MAPK, SAM-pointed domain-containing Ets-like factor (SPDEF)-regulated genes, or the action of adenosine triphosphate (ATP), which is released from RV-infected cells via purinergic P₂ receptors [30,88,89].

2.2.4. RS virus

Serum levels of IP-10 and granulocyte CSF (G-CSF) were elevated in RS-infected children with wheezing [79]. Furthermore, serum IL-6, sputum TNF- α , and IL-8 levels, as well as plasma fibrinogen were elevated in patients with RS viral infection-exacerbated COPD [20,83]. By activating NF- κ B and the phosphorylation of MAPK p38, RS virus infection induces the production of IL-6, IL-8, and TNF- α in Hep-2 (a human epithelial type 2 cell line), HTE, and A549 cells [72,90,91]. In addition to cytokines, ROS are released during RS virus infection through NADPH oxidase activation [76].

2.3. Biological activities of viral infection-induced inflammatory mediators

Inflammatory mediators, such as cytokines, have various functions. For example, IL-1 induces the production of inflammatory cytokines and mediators (IL-4, IL-5, IL-6, IL-8, TNF- α , CRP, and IgE), airway remodeling (e.g., hyperplasia of the airway epithelium and subepithelial airway remodeling), eosinophilia, the influx of neutrophils and macrophages, and mucus hypersecretion [92]. IL-6 plays a central role in the cytokine storm in patients with COVID-19 and pandemic-associated influenza virus infection [93,94] (Fig. 1). It has been associated with the severity of COVID-19 [95,96] and influenza virus-induced cytotoxicity [27], as well as RV-induced pathogenesis, such as T lymphocyte activation and B lymphocyte differentiation, and it can also function as an endogenous pyogen [29]. IL-8 is a major neutrophil chemo-attractant in COPD, bronchiectasis, and DPB [97–99]. It stimulates TLR activation in A549 cells and neutrophils [100,101]. IL-4 and IL-5 are also associated with the exacerbation of eosinophilic asthma [102,103].

Angiogenic and growth factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and TGF- β , are induced by RV, influenza, and Middle East respiratory syndrome (MERS)-CoV viruses, and are associated with the pathogenesis of airway remodeling, interstitial lung disease, and ARDS [73,104–106] partly through the enhancement of fibroblast proliferation and vascular permeability [107,108]. Furthermore, ROS and nitrogen species induce airway inflammation, remodeling, hyperresponsiveness, mucus secretion, and cell damage [75,109–112].

3. Effects of medications on viral infection-induced inflammation

3.1. Effects of medications on CoV infection-induced inflammation

3.1.1. Effects of COVID-19 medications

The IL-6 receptor-blocking monoclonal antibody tocilizumab prolonged survival and improved oxygenation in patients with COVID-19 [62] and decreased the 30-day mortality rate [113], although the effects of tocilizumab on mortality were contradicted by other reports [114]. Furthermore, the levels of inflammatory biomarkers, such as IL-6 and CRP, significantly decreased over 14 days after the administration of tocilizumab in patients with severe conditions [62] (Fig. 1, Table 1).

Furthermore, Morrison et al. demonstrated that the levels of CRP were higher in non-survivors of COVID-19 than in survivors and that levels of CRP, ferritin, and LDH decreased after tocilizumab administration in survivors [115]. Alattar et al. reported that treatment with tocilizumab was associated with radiological improvements and reduced ventilatory support requirements in patients with severe COVID-19 and that oral temperature and inflammatory markers, including CRP levels, decreased after treatment with tocilizumab [116]. So, the anti-inflammatory effects of tocilizumab may have clinical benefits in patients with COVID-19 (Fig. 1).

Wang et al. reported that the antiviral drug remdesivir for SARS-CoV-2 was not associated with statistically significant clinical benefits in a study of hospitalized adult patients with severe COVID-19 [117]. However, treatment with remdesivir reduced the risk of hospitalization or mortality rate among non-hospitalized patients with a high risk of COVID-19 progression, including those with diabetes mellitus, obesity, and hypertension [118]. Furthermore, Marrone et al. demonstrated that treatment with a combination of remdesivir and dexamethasone improved the mortality rate compared with dexamethasone alone [119]. Boglione et al. found that treatment with remdesivir was associated with a lower rate of mortality and intensive care unit (ICU) admission and a shorter time of hospitalization in a case-control study [120]. Marrone et al. reported that a rapid and significant decrease in CRP levels was observed at the end of treatment in patients who were treated with a combination of remdesivir plus dexamethasone, suggesting the anti-inflammatory effects of remdesivir [119] (Fig. 1, Table 1). Dezza et al. reported reductions in IL-6 and CRP levels in patients treated with remdesivir [121].

Remdesivir reduced seasonal CoV-induced IL-6 production in African green monkey kidney epithelial Vero E6 cells, human colon adenocarcinoma (HCT-8) cells, and human fetal lung fibroblast (MRC-5) cells [48].

The clinically available oral antiviral drugs, molnupiravir and nirmatrelvir, reduced mortality and hospitalization rates and resulted in earlier and larger improvements in arterial blood oxygen saturation (SpO₂) values in patients with COVID-19 [122–125]. The effects of molnupiravir and nirmatrelvir on the decrease in inflammatory biomarkers in patients with COVID-19 are uncertain; however, Johnson et al. reported the effects of molnupiravir [125]. The decrease

Table 1 – Anti-inflammatory effects of medications for treating coronavirus infection.

Effects	Medications
SARS-CoV or SARS-CoV-2	
Clinical studies	
Reductions in IL-6, CRP, ferritin, and LDH in patients	*Anti-IL-6 antibody: (Price) [62], (Morrison) [115], (Alattar) [116] Anti-SARS-CoV-2 drugs: (Dezza) [121], (Johnson) [125] Combination of anti-SARS-CoV-2 drug plus corticosteroid: (Marrone) [119] Corticosteroids: (Liu) [128], (Prinzón) [129]
Experimental studies	
Modulation of proinflammatory cytokine production	Corticosteroid: (Cinatl) [130]
Modulation of lung damage	Anti-SARS-CoV-2 drug: (Wahl) [49]
HCoV-229E and HCoV-OC43	
Experimental studies	
Modulation of proinflammatory cytokine production	Anti-SARS-CoV-2 drug: (Hsu) [48] Corticosteroid: (Yamaya) [36] β_2 -agonist: (Yamaya) [36] Muscarinic antagonist: (Yamaya) [36]
Additive inhibitory effects of the combination of ICS, LABA, and LAMA on cytokine production	Corticosteroid, β_2 -agonist and muscarinic antagonist: (Yamaya) [36]
Anti-IL-6 antibody, monoclonal IL-6 receptor blocking antibody; CRP, C-reactive protein; HCoV, human coronavirus; ICS, inhaled corticosteroid; IL, interleukin; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LDH, lactate dehydrogenase; SARS-CoV, severe acute respiratory syndrome coronavirus.	

in CRP levels was observed on day 3 after the start of molnupiravir administration and continued until day 29, whereas a reduction in CRP levels was not observed in the placebo group [125] (Fig. 1, Table 1). These findings suggest the efficacy of molnupiravir in modulating systemic inflammation in patients with COVID-19. Furthermore, in an *in vivo* study, molnupiravir inhibited the pathogenic effects of SARS-CoV-2 infection, including the high level of cell debris in the alveolar lumen in mice [49].

3.1.2. Effects of corticosteroids

Treatment with dexamethasone reduced the 28-day mortality of patients with COVID-19 who received either invasive mechanical ventilation or oxygen alone [126]. Furthermore, treatment with ICS reduced hospitalization and mortality rates and increased the resolution of symptoms in patients with COVID-19 who had mild symptoms [127]. The effects of corticosteroids on cytokine production in SARS-CoV-2-infected cells are unclear. However, Liu et al. demonstrated that treatment with a lower dose (≤ 2 mg/kg day) and a higher dose (> 2 mg/kg day) of methylprednisolone reduced IL-6 levels in patients with COVID-19 and pneumonia [128]. Prinzon et al. reported a decrease in the serum levels of inflammatory markers, such as CRP, LDH, and D-dimer, in patients with COVID-19, who were treated with high-dose methylprednisolone followed by oral dexamethasone compared with patients treated with dexamethasone alone [129].

Dexamethasone does not reduce RANTES production in the human monocytic leukemia cell line THP-1 after SARS-CoV infection [64]. In contrast, high-dose hydrocortisone reduces the production of IL-8 and IP-10 in the human colon epithelial cancer cell line Caco 2 infected with SARS-CoV by inhibiting the activation of the cellular transcription factors, activator protein (AP)-1 and NF- κ B [130] (Table 1). The ICS budesonide reduced the production of

proinflammatory cytokines, such as IL-1 β , IL-6, and IL-8, in HCoV-229E-infected HTE and HNE cells by inhibiting NF- κ B activity [36].

However, in contrast to the anti-inflammatory effects of short-term treatment with glucocorticoids, chronic systemic treatment with medium-high doses of glucocorticoids could potentially increase the risk of SARS-CoV-2 infection in patients with chronic inflammatory arthritis, including rheumatic arthritis [131]. Furthermore, chronic use of ICSs has been associated with an increased risk of hospitalization or mortality rate in patients with COVID-19, COPD, and bronchial asthma [132]. These findings suggest that the presence of chronic inflammatory diseases treated with corticosteroids is a risk factor for SARS-CoV-2 infection and hospitalization or mortality associated with COVID-19.

3.1.3. Effects of β_2 -agonists

Although the anti-inflammatory effects of LABAs on patients with COVID-19 have not been reported, the LABA formoterol reduces the proinflammatory cytokines production, such as IL-6 and IL-8, induced by the HCoV-229E in HTE and HNE cells by inhibiting NF- κ B activation, and the combination of formoterol, glycopyrronium, and budesonide additively reduces the production of proinflammatory cytokines [36]. Based on these findings and those described below on the anti-inflammatory effects of LABAs in the presence of viral infection, including influenza, RV, and RS viruses, LABAs may have anti-inflammatory effects on patients with COVID-19.

3.1.4. Effects of muscarinic antagonists

Based on the findings as described in other subsections on the anti-inflammatory effects of LAMAs in the presence of viral infection, LAMAs may also have anti-inflammatory effects on patients with COVID-19.

3.2. Effects of medications on influenza virus infection-induced inflammation

3.2.1. Effects of corticosteroids

Treatment with corticosteroids improved oxygenation and mortality rates in patients with pandemic influenza virus infection [133]. Treatment with dexamethasone improved the survival rates and lung lesions in mice infected with the 2009 pandemic influenza virus [134]. Furthermore, Thomas et al. reported that treating human bronchial epithelial cells with fluticasone or dexamethasone reduced influenza virus infection-induced cytokine production, including that of IL-8 and RANTES [70] (Table 2). In contrast, Bucher et al. reported that fluticasone treatment increased the release of proinflammatory cytokines, such as IL-6, TNF- α , and IFN- γ after influenza virus infection in the lungs of cigarette smoke-exposed mice [135]. Furthermore, increases in the risk of secondary bacterial infection were reported [136,137]. Hence, the efficacy of corticosteroids in treating influenza virus infection remains controversial.

3.2.2. Effects of muscarinic antagonists

Bucher et al. found that LAMA tiotropium reduced the production of IL-6 and TNF- α in mouse lungs infected with the influenza virus [135] (Table 2). The study reported that a reduction in acetylcholine production due to the reduced production of choline acetyltransferase (ChAT) by tiotropium may be associated with a reduction in cytokine production in mice [135]. Furthermore, the reduction in sialic acid synthase (NANS) expression may be associated with a reduction in influenza virus replication and the subsequent inhibition of cytokine production [135] because NANS induces the expression of sialic acid, a receptor for influenza virus [138,139]. A study has also found that tiotropium decreased the number of total cells, neutrophils, and macrophages in the bronchoalveolar lavage fluid (BALF) of virus-infected mice [135].

3.2.3. Effects of neuraminidase inhibitors

Nasal lavage levels of IL-6, TNF- α , IFN- γ , and monocyte chemotactic protein-1 (MCP-1) were increased in individuals who were experimentally infected with the influenza virus and correlated with the severity of symptoms, including upper and lower respiratory (such as sore throat and cough) and

systemic symptoms (such as fever) [140], and treatment with zanamivir [140] or oseltamivir [141] reduced the levels of these cytokines (Fig. 1, Table 2).

The use of neuraminidase inhibitors (oseltamivir, zanamivir, laninamivir, and peramivir) in influenza virus-infected HTE cells reduced the release of IL-6 and TNF- α [47] (Table 2). Also, zanamivir reduced nitric oxide (NO) production in influenza virus-infected macrophages [142] (Fig. 1, Table 2).

3.2.4. Effects of mucolytic agents

N-acetylcysteine (NAC) inhibits NF- κ B activity and MAPK p38 to reduce the production of IL-6, IL-8, IP-10, TNF- α , RANTES, and MUC5AC in influenza virus-infected A549 cells as well as monocyte migration toward the supernatants of virus-infected A549 cells [71,72] (Fig. 1, Table 2). Similarly, L-carnocysteine reduces influenza virus infection-induced production of IL-1 β , IL-6, and IL-8 in HTE cells by inhibiting NF- κ B activity [143].

3.2.5. Effects of macrolides

Clarithromycin reduces the production of inflammatory cytokines, including IL-1 β , IL-6, and IL-8, in HTE cells infected with the influenza virus by inhibiting NF- κ B activation [68]. Clarithromycin also suppresses the production of MCP-1 and matrix metalloproteinase-9 (MMP-9) and improves pathological changes in the lungs of influenza A virus-infected mice [144]. It increases mucosal antiviral secretory immunoglobulin A induction in the airways of influenza virus-infected mice [145]. Thus, macrolides may modulate influenza virus infection-induced airway and lung inflammations.

3.3. Effects of medications on RV infection-induced inflammation

3.3.1. Effects of corticosteroids

Serum IL-5, IL-6, and ECP levels were reduced in RV infection-induced acute asthma exacerbations after treatment with systemic corticosteroids [79]. Corticosteroids, including dexamethasone and ICSs (budesonide and fluticasone), inhibit RV infection-induced production of inflammatory mediators and growth factors, including IL-6, IL-8, RANTES, IP-10, VEGF, and FGF, in BEAS-2B, primary human bronchial epithelial, and HTE cells [33–35,70,83,104,146] by inhibiting

Table 2 – Anti-inflammatory effects of medications for treating influenza virus infection.

Effects	Medications
Experimental studies	
Reductions in proinflammatory cytokine levels in nasal lavage fluid	Neuraminidase inhibitors: (Fritz) [140], (Hayden) [141]
Reduction in the number of inflammatory cells in BALF	Muscarinic antagonist: (Bucher) [135]
Modulation of proinflammatory cytokine production	Corticosteroid: (Thomas) [70] Muscarinic antagonist: (Bucher) [135] Neuraminidase inhibitors: (Yamaya) [47] Mucolytic agents: (Geiler) [71], (Mata) [72], (Yamaya) [143] Macrolide: (Yamaya) [68]
Modulation of mucin production	Mucolytic agent: (Mata) [72]
Modulation of MCP-1 and MMP-9 production	Macrolide: (Takahashi) [144]
Modulation of NO production	Neuraminidase inhibitor: (Kacergius) [142]
BALF, bronchoalveolar lavage fluid; MCP-1, monocyte chemotactic protein-1; MMP-9, matrix metalloproteinase-9; NO, nitric oxide; SARS-CoV, severe acute respiratory syndrome coronavirus.	

NF- κ B activity [35] or by modulating glucocorticoid responsive elements within the IL-6 promoter [83] (Fig. 1 and Table 3).

Furthermore, Wang et al. demonstrated that fluticasone inhibited RV infection-induced production of MUC5AC in human bronchial epithelial cells by modulating SPDEF-regulated genes and extracellular ATP release [88] (Fig. 1). These findings imply that corticosteroids have anti-inflammatory effects on the airways during RV infection.

3.3.2. Effects of β_2 -agonists

The effects of LABAs in the presence or absence of ICS on the RV infection-induced production of proinflammatory cytokines have been examined. For example, the LABA formoterol reduced the RV infection-induced production of IL-8 and FGF [34] (Table 3). Furthermore, the combination of budesonide plus formoterol and budesonide plus salmeterol had additive or synergistic effects on the suppression of RV-induced IL-8, RANTES, IP-10, and VEGF production [34,104]. Edwards et al. demonstrated that the LABA salmeterol and the short-acting β_2 -agonist (SABA) salbutamol enhanced RV-induced IL-6 production [83]. However, the group also reported that treatment of BEAS-2B cells with a combination of salmeterol and fluticasone reduced IL-8 and RANTES production compared with fluticasone alone after RV16 infection [33]. Moreover, we demonstrated that treatment with the combination of formoterol plus budesonide reduced IL-8 production compared with budesonide alone in RV14-infected primary HTE cells [35] (Fig. 1, Table 3). Furthermore, treatment of RV-infected HTE cells with the combination of formoterol plus budesonide reduced NF- κ B activation compared with budesonide alone [35]. Similarly, Edwards et al. demonstrated that salmeterol alone reduced RV-induced RANTES and IP-10 production in primary bronchial epithelial cells and that the combination of salmeterol plus fluticasone reduced the production of IL-8, RANTES, and IP-10 [33]. The SABA procaterol and the LABA

tulobuterol reduced the RV14 infection-induced release of cytokines from HTE cells [147,148] by inhibiting NF- κ B activation.

3.3.3. Effects of muscarinic antagonists

Treatment of HTE cells with tiotropium reduces the RV14 infection-induced production of proinflammatory cytokines, such as IL-6 and IL-8, by inhibiting NF- κ B activity [37] (Table 3). Wang et al. also found that tiotropium inhibited the RV infection-induced production of MUC5AC in human bronchial epithelial cells without affecting viral replication. However, unlike the effects of fluticasone, the mechanisms were unclear because tiotropium did not modulate SPDEF-regulated genes and extracellular ATP release [88] (Fig. 1).

3.3.4. Effects of mucolytic agents

Mucolytic agents like NAC, L-carbocysteine, and ambroxol, reduce RV infection-induced production of proinflammatory cytokines like IL-1 β , IL-6, IL-8, IL-33, and TNF- α , as well as MUC5AC in HTE, HNE, A549, and human pulmonary mucopidermoid carcinoma NCL-H292 cells, partly by inhibiting NF- κ B or MAPK activity [38,71,72,89,143,149–151] (Fig. 1, Table 3).

3.3.5. Effects of macrolides

Treatment of HTE and HNE cells with erythromycin or clarithromycin reduces RV infection-induced production of IL-1 β , IL-6, IL-8, IL-33, and TNF- α by inhibiting NF- κ B activation [152,153]. Furthermore, treatment of HTE cells with erythromycin reduces RV infection-induced MUC5AC production by inhibiting the Src-related p44/42 MAPK pathway [154]. (Table 3).

3.3.6. Effects of kampo medicines

Hochu-ekki-to and kakkonto reduce RV infection-induced production of cytokines, such as IL-1 β , IL-6, IL-8, and TNF- α , in HTE and HNE cells [155,156].

Table 3 – Anti-inflammatory effects of medications for treating rhinovirus infection.

Effects	Medications
Clinical studies	
Reductions in serum levels of IL-5, IL-6, and ECP	Corticosteroids: (Kato) [79]
Experimental studies	
Modulation of proinflammatory cytokine production	Corticosteroids: (Edwards) [33], (Skevakaki) [34], (Yamaya) [35], (Thomas) [70], (Edwards) [83], (Suzuki) [146] β_2 -agonists: (Edwards) [33], (Skevakaki) [34], (Yamaya) [35], (Yamaya) [147], (Yamaya) [148] Muscarinic antagonist: (Yamaya) [37] Mucolytic agents: (Yasuda) [38], (Geiler) [71], (Mata) [72], (Shishikura) [89], (Yamaya) [143] (Yamaya) [149], (Aizawa) [151] Macrolides: (Suzuki) [152], (Yamaya) [153] Kampo Medicines: (Yamaya) [155], (Saito) [156]
Additive or synergic inhibitory effects of the combination of ICS and LABA on the production of cytokines	Corticosteroids and β_2 -agonists: (Edwards) [33], (Skevakaki) [34], (Yamaya) [35]
Modulation of the production of growth factors (VEGF and FGF)	Corticosteroids: (Skevakaki) [34], (Volonaki) [104]
Additive or synergic inhibitory effects of the combination of ICS and LABA on the production of VEGF and FGF	Corticosteroids and β_2 -agonists: (Skevakaki) [34], (Volonaki) [104]
Modulation of mucin production	Corticosteroid: (Wang) [88] Muscarinic antagonist: (Wang) [88] Macrolide: (Inoue) [154]
FGF, fibroblast growth factor; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; VEGF, vascular endothelial growth factor.	

Table 4 – Anti-inflammatory effects of medications for treating RS virus infection.

Effects	Medications
Clinical studies	
Reductions in serum levels of G-CSF	Corticosteroids: (Kato) [79]
Experimental studies	
Modulation of proinflammatory cytokine production	Muscarinic antagonist: (Bucher) [135] Mucolytic agents: (Mata) [72], (Asada) [157] Macrolide: (Asada) [91], (Yamamoto) [158]
G-CSF, granulocyte colony-stimulating factor, RS, respiratory syncytial.	

3.4. Effects of medications on RS virus infection-induced inflammation

Serum G-CSF levels were reduced in RS virus-induced acute asthma exacerbations after treatment with systemic corticosteroids [79] (Table 4). Bucher et al. reported that a reduction in acetylcholine production due to the modulation of ChAT production by tiotropium may be associated with the reduction in the RSV infection-induced cytokine production, including IL-6, TNF- α and IFN- γ , in mice [135].

By inhibiting NF- κ B activity and the phosphorylation of MAPK p38, L-carnocisteine and NAC reduce RS virus infection-induced production of IL-1 β , IL-6, IL-8 TNF- α , and MUC5AC in HTE and A549 cells [72,157] (Table 4).

Furthermore, treatment of HTE cells with clarithromycin reduces RS virus infection-induced production of IL-1 β , IL-6, and IL-8 [91]. Similarly, clarithromycin reduces IL-6, IL-8, RANTES, and IFN- β production in HNE, A549, and BEAS-2B cells infected with RS virus by modulating IFN regulatory factor dimerization and subsequent translocation to the nucleus [158].

4. Conclusions

Although the magnitude and types of effects of medications may differ, the anti-inflammatory effects of medications, including corticosteroids, LABAs, LAMAs, mucolytic agents, antiviral drugs for treating influenza virus infection, COVID-19 medications, macrolides, and Kampo medicines, may be associated with clinical benefits in the treatment of viral infection-induced respiratory diseases by modulating the production of proinflammatory cytokines in airway and lung cells, cell damage, mucus hypersecretion, inflammation-induced airway hyperresponsiveness, and secondary bacterial infection.

Conflict of Interest

Mutsuo Yamaya was a professor at the Department of Advanced Preventive Medicine for Infectious Disease, Tohoku University Graduate School of Medicine, which was funded by

companies, including Taisho Pharmaceutical Co., Ltd., which provided the clarithromycin. Akiko Kikuchi is an associate professor of the Department of Kampo and Integrative Medicine, Tohoku University Graduate School of Medicine, which is funded by Tsumura Co.

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