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Respiratory Virus Infections in Asthma: Research Developments and Therapeutic Advances

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Abstract
In this review, we discuss the latest developments in research pertaining to virus-induced asthma exacerbations and consider recent advances in treatment options. Asthma is a chronic disease of the airways that continues to impose a substantial clinical burden worldwide. Asthma exacerbations, characterised by an acute deterioration in respiratory symptoms and airflow obstruction, are associated with significant morbidity and mortality. These episodes are most commonly triggered by respiratory virus infections. The mechanisms underlying the pathogenesis of virus-induced exacerbations have been the focus of extensive biomedical research. Developing a robust understanding of the interplay between respiratory viruses and the host immune response will be critical for developing more efficacious, targeted therapies for exacerbations. **Conclusion.** There has been significant recent progress in our understanding of the mechanisms underlying virus-induced airway inflammation in asthma and these advances will underpin the development of future clinical therapies.

Key Words: Asthma ▪ Respiratory Viruses ▪ Interferon ▪ Therapy.

Introduction

Asthma is a heterogeneous condition characterised by chronic airway inflammation, variable expiratory airflow limitation, bronchial hyperresponsiveness and variable symptoms including shortness of breath, wheeze and cough (1). As per the Global Asthma Network's Global Asthma Report 2018, the Global Burden of Disease study estimated that approximately 339 million people were affected by asthma in 2016; and asthma was ranked the 16th leading cause of years lived with a disability and 23rd leading cause of premature mortality (2). Common asthma clinical phenotypes include: early-onset allergic asthma, characterised by elevated levels of specific immunoglobulin E (IgE) and type 2 helper T cell (T_H2) cytokines, and associated with other allergic diseases and responsiveness to corticosteroid therapy; late-onset eosinophilic asthma, defined by an eosinophilia that may be refractory to corticosteroids and responsive to anti-interleukin(IL)-5 therapy; exercise-induced asthma, which is associated with activation of mast cells, T_H2 cytokines and cysteinyl leukotrienes; neutrophilic asthma, characterised by sputum neutrophilia and activation of T_H17 immune pathways; and obesity-related asthma, which primarily affects women and in which there is little airway inflammation (3). It has recently been suggested that using multiplex serum assays can help to classify asthma according to the underlying triggers and thus distinguish between allergen- and virus-triggered asthma, which in turn may assist in tailoring personalised therapies (4).

A loss of asthma control or a worsening of symptoms is termed an 'exacerbation', the severity of which is determined by a combination of the clinical history and changes in lung function parameters (5). Exacerbations are associated with not only significantly worse health-related quality of life, but also with marked increases in healthcare-related expenditure for both patients and healthcare systems (6, 7). To prevent and treat exacerbations successfully, understanding their aetiology is critical. Respiratory viral infections are the most common cause of asthma exacerbations and thus a robust understanding of the pathogenic mechanisms underlying virus-induced exacerbations will be vital to facilitate the development of new treatment strategies (8).

This article provides an overview of recent advances in our understanding of the role of respiratory viruses in asthma exacerbations and highlights the latest studies on potential therapies.

Aetiology of Viral Exacerbations of Asthma

Respiratory viral infections remain the most common cause of asthma exacerbations. Studies have previously demonstrated that 80-85% of exacerbations among school aged children with asthma are caused by respiratory viruses (9). Similarly, among adults with asthma, symptomatic colds have been associated with 80% of exacerbations (10) and respiratory viruses have been detected in the sputum of 76% of asthma exacerbation cases in adults (11).

Among the most common causes of viral asthma exacerbations are rhinoviruses (RV), respiratory syncytial virus (RSV), influenza viruses, parainfluenza viruses (PIV), coronaviruses, adenoviruses and human metapneumovirus (Table 1). The number of viral respiratory infections during early life, rather than the specific viral pathogen, appears to be associated with an increased risk of developing asthma during later life (12). RSV bronchiolitis/lower respiratory infection in early life is particularly associated with the development of recurrent wheeze and asthma in later childhood (13), although interestingly recent evidence suggests that RSV prevention during infancy may not necessarily confer protection against subsequent development of asthma (14). RV infection is the most common trigger of viral asthma exacerbations in adults (15). Wheezing with RV co-infection in early life is an even greater risk factor for subsequent asthma (odds ratio 9.8) than wheezing with RSV co-infection (odds ratio 2.6) (16). Recent advances in the diagnosis of respiratory virus infections include the development of a chip containing microarrayed proteins/peptides from RV,

Table 1. Summary of Common Respiratory Viruses that Cause Asthma Exacerbations (18-24)

Virus	Family	Genome	Cell receptor / binding sites	Reference
Rhinoviruses	Picornaviridae	Single-stranded RNA	Major group serotypes (including both A & B species): Intercellular adhesion molecule-1 (ICAM-1)	(18)
			Minor group serotypes (all A species): Low-density-lipoprotein receptor (LDLR)	
			Group C species: Cadherin-related family member 3 (CDHR3)	
Respiratory syncytial virus	Paramyxoviridae	Single-stranded RNA	Nucleolin	(19)
Influenza viruses	Orthomyxoviridae	Single-stranded RNA	Sialic acids	(20)
Parainfluenza viruses	Paramyxoviridae	Single-stranded RNA	Sialic acids	(21)
Coronaviruses	Coronaviridae	Single-stranded RNA	Strain-specific; e.g. SARS-CoV binds to angiotensin-converting enzyme 2 (ACE2), MERS-CoV binds to dipeptidyl peptidase 4 (DPP4)	(22)
Adenovirus	Adenoviridae	Double-stranded DNA	Cell surface integrins αvβ3 and αvβ5	(23)
Human metapneumovirus	Paramyxoviridae	Single-stranded RNA	Cell surface integrin αvβ1	(24)

which has enabled the rapid diagnosis of RV-A and RV-C (far less commonly, RV-B) in serology from a paediatric population with RV-induced wheeze (17).

Deficiencies in Immunological Responses to Viral Infections in Asthma

Evidence for a deficiency in interferon (IFN) responses – Type I IFNs such as IFN-α and IFN-β play an important role in antiviral immune responses. Several studies have demonstrated that the host IFN response to rhinovirus infection is deficient in both asthma and chronic obstructive pulmonary disease (COPD) (25, 26). Initial evidence for this came from work undertaken by Wark and colleagues, in which primary bronchial epithelial cells (BECs) sampled from people with asthma and healthy controls were infected with RV-16. There was a significant impairment in speed of onset as well as magnitude of IFN-β mRNA expression and IFN-β protein production in RV-infected cells from people with asthma compared to RV-infected cells from controls. There was significantly enhanced viral replication in cells from people with asthma compared to healthy controls, but following administration of exogenous IFN-β, viral replication rates were significantly reduced (27). Further work by Contoli and colleagues showed that people with asthma also exhibit deficient production of type III IFNs such as IFN-λ1 and IFN-λ2/3. Relative to healthy controls, there was significant deficiency in induction of these IFNs in BECs and bronchoalveolar lavage (BAL) cells from people with asthma following RV infection (28). Furthermore, IFN-λ production in response to *ex vivo* RV infection of BAL cells sampled before experimental RV infection *in vivo* was strongly related to virus load, airway inflammation and symptom severity during the subsequent *in vivo* infection, strongly implicating IFN deficiency with increased exacerbation severity (28). These findings were reinforced by subsequent studies demonstrating that primary BECs from people with asthma exhibit significantly less IFN-λ production compared to healthy controls following RV-1B infection (29). RV-induced type I and type III IFN responses are significantly diminished in asthmatic subjects irrespective of their atopic status (30). This IFN deficiency is also seen in severe therapy resistant asthmatic children, whose BECs (compared to controls) exhibit a higher viral load that negatively correlates with IFN-β and IFN-λ mRNA levels (31).

Recently, an *in vivo* study demonstrated that there is deficient IFN-α and IFN-β protein expression by BECs in people with asthma compared to controls at baseline. Lower levels of epithelial IFN-α and IFN-β expression were correlated with more severe cold symptoms, worse airway hyperresponsiveness and greater reductions in forced expiratory volume in 1 second (FEV_1) following RV infection. Furthermore, the study showed that deficiency in IFN induction among people with asthma was not associated with deficient pattern recognition receptor (PRR) expression at baseline (32).

It has also been suggested that type I IFN deficiency seen in asthma may depend on the degree of asthma control at the time of sampling and perhaps also on asthma subtype. In a study of adult patients with sub-optimal asthma control, peripheral blood mononuclear cells (PBMCs) were stimulated with RV-1B *in vitro* and IFN responses were measured: PBMCs from patients with neutrophilic asthma exhibited significantly impaired IFN-α production compared to PBMCs from those with eosinophilic asthma and paucigranulocytic asthma, though inhaled steroid dose was also an independent predictor of decreased IFN-α protein production (33).

Measurement of cytokine responses to RV infection of PBMCs from children may offer a way to predict the likely course of asthma in later life. In a recent study, PBMCs from children were stimulated with RV and cytokine production was subsequently measured. The study identified that distinct cytokine immunophenotypes were associated with different clinical trajectories. The greatest risk of developing asthma in later life and of experiencing severe asthma exacerbations was associated with the lowest levels of IFN induction

and high levels of proinflammatory cytokine production in response to RV stimulation of PBMCs. Conversely, the lowest risk of asthma was seen in the group who exhibited moderate IFN induction and the highest induction of proinflammatory cytokines following RV infection of PBMCs (34). These findings have been reinforced by another recent study which showed that neonates whose cord blood cells did not produce any type I or type III IFNs in response to polyinosinic: polycytidylic acid (poly I:C) stimulation had a significantly increased risk of developing febrile lower respiratory infection in the first year of life, as well as a four-fold increased risk of persistent wheeze at age five years, compared to those neonates who produced at least one type I or type III IFN at birth, suggesting an important role for developmental regulation of type I and type III IFN production in subsequent risk of asthma development (35). Novel immunophenotyping in this manner may enable better understanding of the mechanisms underlying virus-induced allergic airways disease in children and in later life.

Further ways of predicting short-term asthma exacerbation risk have been highlighted in a recent transcriptome analysis. This demonstrated that children with high nasal 'type 2 inflammation' module expression and low nasal 'type 1 IFN response' module expression exhibit a faster time to asthma exacerbation; and the most significant risk of exacerbations in the short-term is among those in whom there is an elevated ratio of 'type 2 inflammation' to 'type 1 IFN response'. Diminished IFN signalling at baseline may permit increased viral replication to occur, which in turn promotes asthma exacerbation with enhanced IFN responses during exacerbation, consequent upon increased virus load (36).

Studies not reporting a deficiency in IFN responses in asthma – An extensive discussion regarding studies not reporting a deficiency in type I and/or type III IFN responses in asthma can be found in a recent review (25). Here, we highlight studies not previously described in that review. In a study by Moskwa and colleagues in which human BECs were infected with either PIV type 3 (PIV3) (multiplicity of infection (MOI) 0.1) or RV-1B (MOI 0.1), viral replication rates in BECs were not different between people with asthma or controls for either virus and no differences were observed in IFN-α, IFN-β or IFN-λ1 mRNA or IFN- λ1 protein production between the two groups (37). It is possible that the lack of difference in IFN induction between asthmatic and non-asthmatic cells was related to the MOI used: MOI 0.1 was used in this study whereas the study by Wark and colleagues that demonstrated significant impairment in IFN-β induction in RV-infected asthmatic BECs used MOI 2 (27). Additionally, the BECs in the study by Moskwa and colleagues were derived from a mixture of atopic (N=6) and non-atopic (N=4) asthmatics, whereas most studies reporting impairment in IFN induction in virus-infected asthmatic BECs have used BECs derived from only atopic asthmatics. Indeed, sub-group analysis of the asthma group showed that, compared to atopic asthmatic cells, non-atopic asthmatic cells exhibited lower IFN-λ1 protein and lower IFN-α/IFN-β mRNA in response to PIV3; and lower IFN-β mRNA in response to RV (37). Subject numbers were small (10 asthmatics and 9 healthy controls) and the majority of asthma subjects had mild asthma (37).

A recent study showed that BECs from children who have asthma and obstructive lung function exhibited greater RSV-induced type I and type III IFN expression compared to BECs from children with asthma who had a non-obstructive lung function picture and compared to healthy controls (38). However, this study only assessed IFN responses late at 96hrs after RSV infection (MOI 0.5); thus it is possible that deficient IFN induction early following infection may have enabled greater viral replication during the early phase of infection, which secondarily induced an exaggerated IFN response later during infection. This interpretation is supported by the observation of around 10 times higher RSV copy numbers at 96 hrs in the BECs from children with asthma and obstructive lung function, compared to the healthy control subjects.

Reconciling the discrepancy in the evidence base relating to the IFN response in viral asthma exacerbations will require further study. However,

possible explanations for the seemingly divergent evidence base include that different studies have used different virus strains, different MOI and have studied different time points during infection in subjects with differing severities of asthma and different cell culture conditions (39). Concurrent treatments being taken by study participants may also affect the degree of IFN expression: for example, it has recently been shown that use of inhaled corticosteroid therapy suppresses IFN production in virus-induced exacerbations of COPD, resulting in increased pulmonary bacterial load (40). All these factors, and very likely others as well, may result in heterogeneity in the degree of IFN response that has been measured.

Airway Inflammation in Response to Viral Infections in Asthma

Eosinophils – The role of eosinophils in promoting airways inflammation in patients with allergic asthma is well established. The antiviral effects of eosinophils have previously been attributed to secreted effector proteins including eosinophil-derived neurotoxin (41), which exhibits RNAse activity (42). Human eosinophils treated with a nitric oxide synthase inhibitor have a diminished antiviral effect against PIV, suggesting that nitric oxide likely plays a role in eosinophils' anti-infective activity (43). Additionally, transfer of eosinophils from MyD88-deficient mice to wildtype mice results in the recipient mice having higher RSV loads, suggesting that the antiviral properties of eosinophils may be contingent on the toll-like receptor (TLR) -7/MyD88 signalling pathway (44). Transferring eosinophils from allergen-sensitised mice into influenza A virus-infected mice has been shown to reduce virus load and improve lung compliance in the infected mice, suggesting that eosinophils may confer a protective effect against respiratory viral infections (45). An *in vivo* study has demonstrated the ability of pulmonary eosinophils to internalise and inactivate influenza virus in mice and the ability of blood eosinophils from healthy human subjects to similarly capture and inactivate RSV and influenza virus. This capability of eosinophils was found to be significantly diminished in patients with asthma and greater asthma severity was associated with a greater reduction in virus capture by eosinophils (46). It should be noted that anti-IL-5 therapies, which target IL-5 or the IL-5 receptor and thus reduce eosinophil numbers/activation, have been shown to reduce the frequency of clinically significant exacerbations in people with asthma and eosinophilia (47). Relevant clinical trials are discussed later in this review.

IL-33 – Use of novel mucosal sampling techniques such as nasosorption and bronchosorption have demonstrated that there is marked local induction of IFNs and T_H2 responses in the upper and lower airways of asthma patients following RV infection (48). RV infection induces IL-33 and a T_H2 cytokine response in the airways of asthma patients, with IL-33 levels correlating with IL-5 and IL-13 levels. Blockade of the IL-33 receptor abolishes RV-induced T_H2 cytokine production by human T cells and type 2 innate lymphoid cells, suggesting that IL-33 plays an integral functional role in promoting the T_H2 inflammatory response to RV infection in asthma (49). This is further reinforced by a study in sensitised mice which has shown that IL-33 suppresses innate antiviral responses and adaptive T_H1 responses in influenza-induced exacerbations, thus promoting enhanced airway inflammation (50). Administration of anti-IL-33 therapy in sensitised mice that have been exposed to RV decreases the T_H2 immune response throughout the course of the subsequent disease, decreases exacerbation severity and promotes expression of IFN-α, IFN-λ and IFN-γ. However, it has no effect on airway smooth muscle remodelling during the chronic phase of disease (51).

It has been suggested that the cellular immune response to IL-33 following RV infection differs between people with asthma and healthy individuals. A study in which PBMCs from subjects with allergic asthma and healthy controls were co-stimulated with IL-33 and RV showed that while IL-33 augmented RV-induced IL-5 and IL-13 production in PBMCs from asthma patients, it had no effect on IL-5 and IL-13 production in PBMCs from healthy

controls. Additionally, IL-33 promoted innate lymphoid cell production of IL-13 in PMBCs from asthma patients but promoted natural killer cell production of IFN-γ in PBMCs from controls (52).

Transcriptome network analysis of nasal and blood samples from children with virus-induced exacerbations has also shown that there is upregulation of the *IL33* gene among this group compared to those who have had non-viral exacerbations (36). A study of virus-induced asthma exacerbation using wildtype and IL-1β knockout mice has shown that IL-33 expression upon virus inoculation is contingent on the IL-1β signalling pathway, with the latter also shown to promote expression of neutrophil chemoattractants and the mucin MUC5AC (53).

IL-25 – IL-25 regulates T_H2 responses and has been shown to contribute to the pathogenesis of allergic asthma (54). More recently, its role in RV-induced asthma exacerbations has been elucidated. Compared to RV infection of BECs from healthy controls, RV infection of BECs from people with asthma *in vitro* resulted in significantly greater *IL25* mRNA expression at 8 hours post-infection and greater IL-25 protein expression at 24 hours post-infection (55). In the same report, human experimental RV infection showed that relative to baseline, subjects with asthma exhibited a significant increase in IL-25 protein concentrations in nasal mucosal lining fluid following RV infection *in vivo*, whereas healthy controls exhibited a more modest increase. Additionally, in mouse models of virus-induced exacerbation of allergic airways disease, RV-induced IL-25 expression was associated with enhanced T_H2 cytokine induction, while IL-25 receptor blockade resulted in a reduction in T_H2 responses and MUC5AC production. Thus IL-25 plays a key role in the pathogenesis of virus-induced allergic airways inflammation (55).

IL-18 – RV infection has recently been shown to induce IL-18 in humans *in vivo*, both among people with asthma and healthy controls. Regardless of asthma status, individuals with a low baseline nasal IL-18 level developed more severe colds following RV infection than those individuals with a high baseline nasal IL-18 level, suggesting that airway mucosal IL-18 levels prior to RV infection may serve as an important predictor of symptom severity following RV inoculation. This suggests that IL-18 may have a protective effect against RV infection of the respiratory tract, although the mechanisms underlying this effect remain unclear (56).

Neutrophil Extracellular Traps (NETs)

Neutrophils have been shown to exert a protective effect against respiratory tract infections caused by influenza virus, as evidenced by enhanced viral replication in influenza-infected neutrophil-depleted mice (57). Studies have previously demonstrated that RV infection in people with asthma is associated with a significant increase in the number of bronchial epithelial and subepithelial neutrophils; and that the bronchial neutrophil count is positively associated with the RV virus load (58). While the process of neutrophil recruitment, phagocytosis and release of toxic granules is well established, recent attention has shifted to how neutrophil extracellular traps (NETs) contribute to inflammation in respiratory disease (59).

NETs, which comprise double-stranded DNA (dsDNA), histones and granular proteins, are released by neutrophils into the extracellular space and stimulate a T_H2 immune response (60). NETs have been identified in bronchial biopsies from people with mild allergic asthma (61) and high concentrations of NETs in the sputum are associated with more severe asthma, characterised by low Asthma Control Test scores, mucus hypersecretion and frequent use of oral corticosteroids (62). NET formation may be stimulated by neutrophil exposure to virus: RSV fusion protein has been shown to interact with TLR4 on neutrophils and thereby trigger NET formation (63). A role for NETs in driving the severity of RV-induced asthma exacerbations has recently been demonstrated: RV infection of subjects with asthma resulted in significant release of host dsDNA in nasal lavage samples and this correlated with symptom severity and bronchial concentrations of the T_H2 cytokines IL-5 and IL-13. Reducing the level of dsDNA in the airways of RV-infected allergic mice using DNase

and inhibition of NET formation using an elastase inhibitor resulted in a decrease in bronchoalveolar lavage fluid eosinophils, lymphocytes and mucins as well as lung T_H2 lymphocytes and cytokines with a reduction in RV-exacerbated airway hyperresponsiveness and airway inflammation (64).

Therapeutic Developments

Given the significant health and socioeconomic impact of viral asthma exacerbations, robust prevention and treatment strategies are needed.

Potential biomarkers – In a study of patients with asthma who were steroid-naïve, serum IFN-γ-induced protein 10 (IP-10; also known as CXCL10) levels were shown to be higher among those with virus-induced asthma compared to those with non-viral exacerbations; serum IP-10 levels had a sensitivity of 95% and specificity of 70% for virus-induced asthma (65). An observational study has demonstrated that serum IgG concentration taken at the time of hospital admission among patients with confirmed virus-induced severe asthma exacerbations is significantly lower than the admission serum IgG concentration among those admitted with non-viral asthma exacerbations. Low serum IgG at the time of admission is associated with longer duration of oral corticosteroids and hospital stay. However, statistical analysis demonstrated that serum IgG concentration had poor specificity and modest sensitivity for predicting the severity of asthma exacerbations, suggesting that the clinical utility of measuring this requires further study (66).

Vaccinations – There remains limited evidence on how efficacious respiratory virus vaccinations are at decreasing the rate of viral exacerbations in asthma patients. A Cochrane systematic review of influenza vaccination in people with asthma demonstrated that there was no reduction in influenza-induced asthma exacerbations among children; however, children who had been vaccinated had better symptom scores during influenza-positive weeks. Studies in adults did not contribute useful data due to very low levels of confirmed influenza infection (67). However, in a subsequent systematic review and meta-analysis which included robust quasi-experimental and epidemiological studies in addition to randomised controlled trials, it was shown that influenza vaccination may prevent up to 78% of asthma attacks that necessitate unscheduled emergency hospital visits (68). Although there is evidence to suggest that administration of a recombinant VP0 capsid protein RV vaccination in mice promotes more effective RV clearance following RV challenge (69), the considerable heterogeneity in human RV strains means that developing clinically effective vaccinations remains a challenge and there are still no approved vaccinations against RV for use in humans.

Antiviral agents –Targeting the cellular receptors of viruses offers a potential therapeutic target. RV major group serotypes bind to intercellular adhesion molecule 1 (ICAM-1), which is a leukocyte adhesion molecule (70) that serves as a receptor for RV (71). Blocking such cellular adhesion molecules, which otherwise regulate immune cell function and migration, may offer a way of reducing inflammation (72). Blockade of ICAM-1 by a novel anti-human ICAM-1 antibody (14C11) has been shown to reduce airway inflammation following infection with RV-14 and RV-16 in a mouse model (73). The use of recombinant soluble ICAM-1 (tremacamra) in humans has been shown to reduce the severity of RV infection symptoms compared placebo control (74), but the high frequency of dosing required prevented further clinical development. Various drugs targeting the RV capsid have been studied: intranasal pirodavir was found to have a significant antiviral effect but did not provide clinical improvement in cold symptoms (75); oral pleconaril reduced the duration of cold symptoms by one day compared to placebo (76), but was associated with bleeding in women taking oral contraceptives and was rejected by the US Food and Drug Administration (77); and vapendavir had an antiviral effect but did not provide an improvement in lung function or reduction in asthma exacerbations in patients with RV infection (78).

Macrolide antibiotics – Studies have suggested that macrolides have a beneficial effect when used in the treatment of asthma exacerbations:

for example, telithromycin has been shown to significantly reduce exacerbation symptoms (79). However, the mechanisms underlying the beneficial effects of macrolides remain unclear. Studies have suggested that macrolides may exhibit antiviral properties by restoring deficient IFN responses and attention has turned to utilising this in the treatment of viral asthma exacerbations. Azithromycin has been shown to augment RV-1B and RV-16 induced IFN production in human BECs while decreasing RV replication in vitro; this effect was not seen with telithromycin (80). In a randomised controlled study in adult patients with asthma, azithromycin treatment did not result in a significant improvement in asthma symptoms scores compared to placebo; however, interpretation of this study is difficult as for every patient randomised, more than 10 were excluded for having already received antibiotics (81). Among children aged 1 – 3 years, azithromycin has been shown to significantly reduce the duration of asthma-like symptoms compared to placebo, with reductions being greater among those who were started on therapy before the sixth day of symptoms (82). Among children with a history of recurrent severe lower respiratory tract infections (LRTIs), early use of azithromycin during a LRTI significantly reduces the risk of a clinically severe LRTI developing (83). Several novel macrolides that are derivatives of azithromycin, erythromycin and oleandomycin have also been shown to augment IFN responses in BECs that have been infected with RV *in vitro* and one has been shown to have anti-viral activity in BECs from people with asthma (84).

Inhaled IFN therapy – Given the evidence for IFN deficiency in the pathogenesis of virus-induced asthma exacerbations, a randomised double-blind placebo-controlled study was undertaken to evaluate the clinical effectiveness of administering a 14-day regimen of inhaled IFN-β therapy following onset of cold symptoms in asthma patients. Although the therapy did not have a significant effect on the primary endpoint of patient-reported symptoms, sub-group analysis showed that it did improve reported symptoms among people with moderate to severe asthma. Additionally, treatment with inhaled IFN-β was associated with an improvement in morning peak expiratory flow and enhanced expression of antiviral biomarkers such as serum CXCL10 and sputum CXCL10, Mx1 and OAS1 (85). Thus, inhaled IFN-β therapy may ameliorate virus-induced symptoms in those with moderate to severe asthma, but further confirmatory studies are needed. In a recent *in vitro* study, monocyte-derived macrophages, alveolar macrophages and primary BECs from healthy controls and COPD patients were infected with influenza virus either before or after administration of exogenous IFN-β. Cell infection was significantly reduced in all three cell types when IFN-β was administered prior to influenza infection, but this effect was not present when administered post-influenza infection. This suggests that prophylactic IFN-β therapy may be of utility in reducing respiratory tract viral infections; additional *in vivo* clinical studies are needed to evaluate this further (86).

Anti-IgE therapy – The clinical utility of anti-IgE therapies in severe allergic asthma is well-established (87). The potential for such therapies to treat and shorten the duration of virus-induced exacerbations has shown promise. In a paediatric allergic asthma population, the use of omalizumab as a treatment adjunct for virus-induced exacerbations has been shown to reduce the duration of RV infections by approximately 1 day, reduce peak viral shedding and decrease the frequency of RV illnesses (88). In another paediatric study, omalizumab significantly decreased the severity of RV-induced asthma exacerbations, even among patients who started with a poorer baseline disease activity (89). The beneficial effect of omalizumab in treating virus-induced exacerbations may be due to its effect on IFN-α production. In a recent study, PBMCs and plasmacytoid dendritic cells (pDCs) were isolated from children with recurrent asthma exacerbations, both before and during treatment with omalizumab (90). The PBMCs and pDCs were stimulated *ex vivo* with either RV or influenza virus and IFN-α protein production was subsequently measured. Relative to pre-omalizumab treatment, omalizumab treatment (in the presence of IgE cross-linking) significantly increased IFN-α

production by 2.06-fold in RV-treated PBMCs, 1.57-fold in influenza-treated PBMCs and 4.15-fold in RV-treated pDCs (90). This reinforces previously reported data showing that omalizumab improved peripheral blood mononuclear cell generation of IFN-α in response to RV among children with asthma; and that, among the omalizumab group, greater IFN-α increases were associated with significantly fewer exacerbations (91).

Anti-IL-5 therapy – The clinical utility of anti-IL-5 therapy in the prevention of exacerbations in severe eosinophilic asthma has been established (92). Given the potential role of eosinophils in virus-induced exacerbations, a recent study has investigated the therapeutic value of using anti-IL-5 therapy in mild asthma to attenuate the eosinophil-mediated immune response to RV-16 infection. While administration of mepolizumab did diminish baseline blood and tended to diminish sputum eosinophil counts, it did not cause a significant improvement in lung function or in fractional exhaled nitric oxide after RV challenge, nor did it prevent eosinophil activation following RV-16 inoculation (93). Benralizumab has been shown to reduce annual asthma exacerbation rates and improve prebronchodilator FEV_1 among patients with severe, uncontrolled asthma and eosinophilia (94). Reslizumab has been shown to reduce frequency of asthma exacerbations among patients with inadequately controlled, moderate-to-severe asthma and eosinophilia (95). While virology testing was not performed in these latter two studies, it is likely that many of the asthma exacerbations would have been viral in origin.

Anti-IL-13 therapy – Lebrikizumab, a humanized IgG_4 anti-IL-13 monoclonal antibody, has been shown to reduce exacerbation frequency by 60% and improve lung function in patients with moderate to severe asthma who have high levels of serum periostin (96). A subsequent study has demonstrated that lebrikizumab reduces exacerbation rates among patients with uncontrolled asthma who have high periostin levels or high blood eosinophil counts, but these effects were not consistently observed in the replicate study (97). In contrast, a phase 2b study of tralokinumab, a fully human IgG_4 anti-IL-13 monoclonal antibody, showed that it did not significantly reduce exacerbation rates in patients with severe asthma compared to placebo, although there may be an improvement in exacerbation frequency and symptom control in those with high serum periostin and high serum dipeptidyl peptidase 4 (DPP4) levels (98). A recent study has also shown that tralokinumab has an inconsistent beneficial effect on annualised asthma exacerbation rates among severe asthmatics with high baseline fractional exhaled nitric oxide (FeNO; a non-invasive surrogate marker of airway inflammation in patients with asthma (99)) (100).

Anti-IL-4/13 therapy – Dupilumab, a monoclonal antibody against the α subunit of the IL-4 receptor which inhibits both the IL-4 and the IL-13 signalling pathways, reduces exacerbation rates and improves lung function in moderate to severe eosinophilic asthmatics when long-acting β_2-agonist/steroid combination therapy is withdrawn (101). Recently, a study among patients with uncontrolled asthma demonstrated that administration of dupilumab results in a significant reduction in annualised rates of severe asthma exacerbations and a significant increase in FEV_1 compared to matched placebo controls, with the greatest clinical benefits being observed among those with a higher baseline blood eosinophil count (102).

PRR Antagonism – PRRs activated by RV infection include TLRs such as TLR3, melanoma differentiation-associated gene 5 (MDA5) and retinoic acid-inducible gene I (RIG-I) (103, 104). Based on pre-clinical model data, it was hypothesised that blockade of TLR3 and its downstream signalling pathways may offer a novel way in which to diminish the inflammatory effect of RV infection in asthma. In a randomised controlled study in asthma patients, the use of CNTO3157, an inhibitory anti-TLR3 monoclonal antibody, was found to be ineffective at protecting against symptoms or decreases in FEV_1 following RV inoculation and its use was associated with a greater number of post-inoculation moderate and severe exacerbations compared to those receiving placebo (105). TLR3 inhibition has been shown to de-

crease IFN-λ production in airway epithelial cells that have been stimulated with the TLR3 agonist poly I:C (106). It is therefore possible that TLR3 blockade with CNTO3157 dampened the IFN response following RV inoculation, thus permitting increased viral replication which in turn triggered more exacerbations.

CXCR2 receptor antagonists – Neutrophil activation and migration are regulated by the CXCR2 receptor. The potential to block neutrophil inflammatory pathways by using CXCR2 receptor antagonists in asthma has been under investigation for some time. In a randomised placebo-controlled trial involving patients with severe asthma, the CXCR2 antagonist SCH527123 was shown to significantly reduce sputum neutrophil count and tended (P=0.05) to reduce mild exacerbation frequency (107). However, in a separate trial using the CXCR2 antagonist AZD5069 in patients with uncontrolled persistent asthma, there was no effect on the frequency of severe exacerbations (108). The therapeutic value of utilising such drugs to target NETopathic inflammation in virus-induced asthma exacerbations remains to be seen (109).

Conclusions

Respiratory virus infections play an integral role in the pathogenesis of asthma exacerbations. In recent years, studies have shed further light on the potential mechanisms underlying the interactions between respiratory viruses and the immune system. There is substantial evidence suggesting deficiencies in the host immune response may predispose many asthma patients to virus-induced exacerbations. There have been several recent advances in our understanding of the mechanisms underlying virus-induced airway inflammation in asthma, including growing evidence around the role of pro-inflammatory cytokines such as IL-33, NETs, eosinophils and the interaction between viruses and bacterial infections. Developing a more robust understanding of these mechanisms will be critical for developing novel and more efficacious therapies to prevent and treat virus-induced asthma exacerbations.

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