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# Anti-viral agents: potential utility in exacerbations of asthma

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Asthma is the most common chronic respiratory disease and its prevalence is on the increase. Respiratory viral infections in early life have been suggested to increase the risk of development of asthma in later life and virus infection remains the single greatest precipitant of asthma exacerbations. The development of effective anti-viral treatments remains a key target for therapeutic intervention. Here we discuss the role of respiratory viral infection in asthma exacerbation and highlight current and potential anti-viral agents and their mechanisms of action.

## Addresses

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## Introduction

Asthma is a heterogeneous airway disease characterised by airway inflammation, airway hyperreactivity, reversible bronchoconstriction and airway remodelling. Patients experience shortness of breath, fluctuations in normal breathing patterns, and also periodic episodes of wheeze and cough. Asthma is treated with inhaled corticosteroids, with and without other therapies including short or long acting bronchodilators. Asthma exacerbations (AEs) are the major cause of morbidity, mortality and healthcare costs associated with asthma [1,2], and are generally defined as worsening of the above symptoms accompanied by a drop in lung function prompting a GP consultation or visit to the emergency room. In extreme cases, AE can require oral

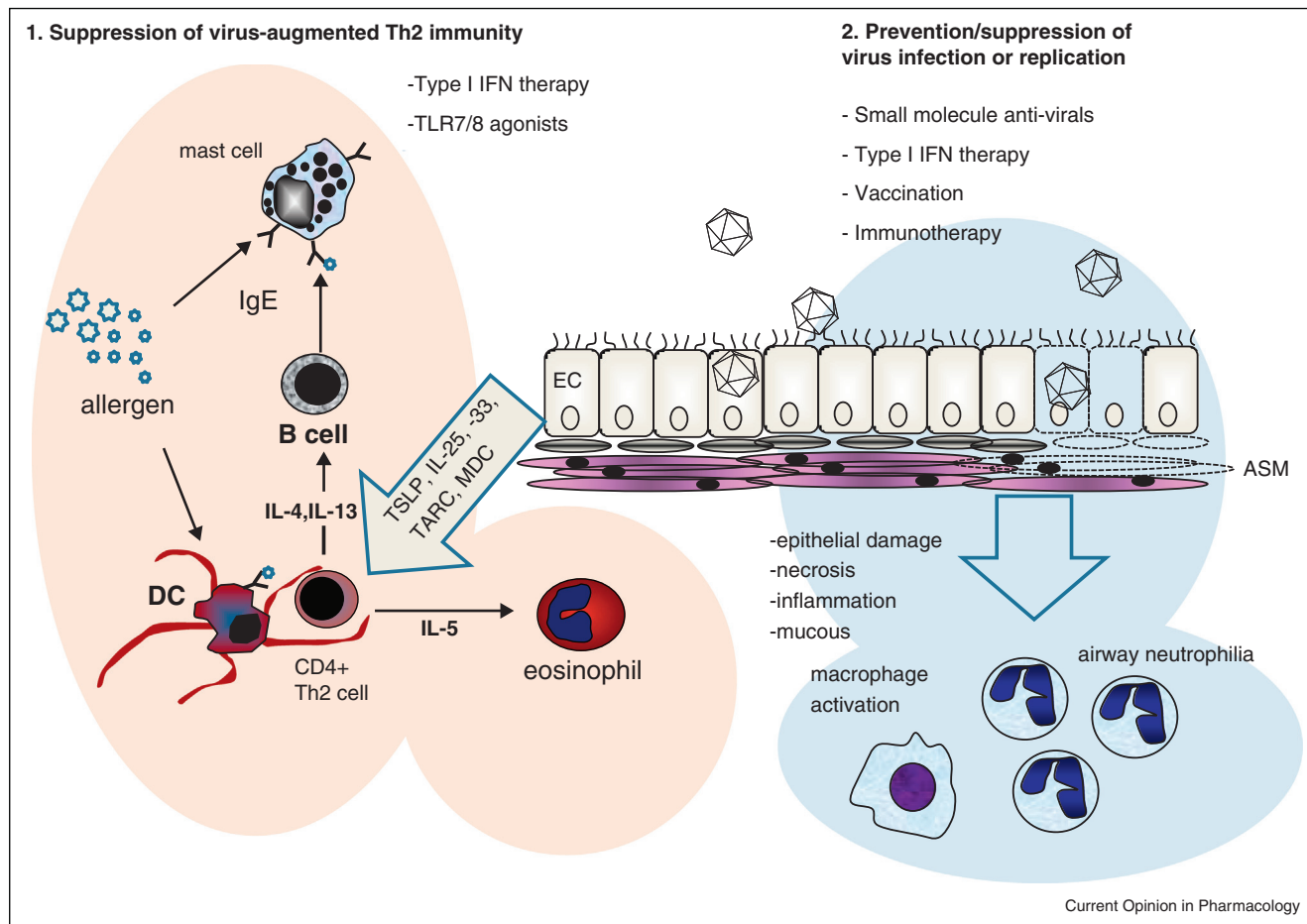
corticosteroid therapy, supplemental oxygen and may result in death. Respiratory virus infections account for at least 80% of exacerbations in adults and children [3–6] and among respiratory viruses human rhinoviruses (RVs) are by far the most common viruses associated [3,6,7].

The importance of respiratory viruses as triggers of AE has therefore made them a target for therapeutic intervention. In this review we discuss the potential of two therapeutic approaches, one targeting host factors that may induce natural anti-viral immunity, such as the addition of an anti-viral cytokine, manipulation of the host's immune response such as administration of a vaccine, and secondly targeting the virus itself; including small molecule inhibitors of virus replication, and virus specific immunotherapy. These approaches are summarised in [Figure 1](#). Because of the overwhelmingly important role viruses play in AE, we argue that now is the time to carefully re-consider anti-viral interventions for AE.

## Respiratory viruses are potent exacerbators of asthma

Respiratory virus infections are triggers of AE. Viruses such as RVs, respiratory syncytial virus (RSV), seasonal influenza A viruses, metapneumoviruses, coronaviruses and bocaviruses may all trigger AE in adults and children. Atypical bacteria *Mycoplasma pneumoniae* (*M. pneumoniae*) and *Chlamydophila pneumoniae* (*C. pneumoniae*) are also common respiratory pathogens associated with AEs in both adults and children [8–10]. The major viruses associated with AEs are RVs, accounting for approximately 60% of all AE in all ages [6,7]. RVs are members of the *Picornaviridae*, and are positive sense ssRNA viruses with genomes of 7.1–7.5 kb and can be divided into major and minor groups based on receptor utilisation. Major group RVs bind ICAM-1 while minor group RVs bind the LDL receptor. RVs may also be classified based on nucleotide sequence identity (RV-A, RV-B, RV-C). The RV-C group [11•,12] have unique sequences at the ICAM-1 and LDL receptor binding sites, suggesting they use a unique, currently unknown receptor [13•]. RVs represent a diverse group of viruses with 100 serotypes known and an estimated further ~60 or so group C viruses. RV-C may cause more severe AEs, although how this occurs is currently unknown [12]. In the northern hemisphere, RV infection precipitates an increase in emergency room admissions due to AEs [14], known as the 'asthma epidemic.' This occurs in the third week of September, after children return to school, highlighting that school age

Figure 1



Anti-viral approaches may **(1)** prevent viruses acting in a synergistic or additive manner with allergens, and cause immune deviation to a Th1 rather than Th2 immune response. Anti-viral approaches may be **(2)** agents that prevent virus infection or replication at mucosal surfaces and prevent epithelial damage, inflammation, mucus production, activation of macrophages and attraction of neutrophils into the lung, which promote further inflammation and damage.

children are vectors for RV infection and their crucial role in AEs [7]. Major and minor group RV mouse models of RV infection [15<sup>••</sup>,16] and RV induced exacerbations of airway allergen challenge [15<sup>••</sup>,17] have also recently been developed. These animal studies mirror the human data gathered to date and support the idea that RV infection augments airways inflammation caused by allergen sensitisation and challenge, providing further evidence that respiratory viruses such as RV exacerbate asthma.

## Targeting host factors

### Type I IFN therapy

Recent studies have reported that impaired innate immunity to virus infections is important in the pathogenesis of AEs. Reduced capacity to induce type I interferons (IFNs) IFN- $\alpha$ , IFN- $\beta$  or type III IFNs, the IFN- $\lambda$ s upon challenge with respiratory viruses or the dsRNA mimetic polyIC in bronchial epithelial cells

(BECs), bronchoalveolar lavage (BAL) macrophages, dendritic cells (DCs) and peripheral blood mononuclear cells (PBMCs) from persons with asthma have recently been described [18<sup>•</sup>,19,20<sup>••</sup>,21,22<sup>•</sup>,23,24<sup>••</sup>,25<sup>••</sup>,26<sup>••</sup>]. Importantly, deficient IFN- $\lambda$  was also strongly related to virus load, and AE pathogenesis and severity *in vivo* [22<sup>•</sup>]. The mechanism responsible for impaired IFN- $\alpha$ , IFN- $\beta$  and IFN- $\lambda$  remains poorly understood. However, the above studies advocate a role for IFN therapy in AE. Recently, a phase II placebo controlled trial of inhaled IFN- $\beta$  in poorly controlled adult atopic asthmatics was performed [27]. Inhaled IFN- $\beta$ , started at the reporting of a clinical cold, showed promise, reducing rates of AE in this group and increasing lung function. Virus load was studied in only a few patients, and showed trends for lower virus loads in treated patients. Therefore, inhaled IFN- $\beta$  improves AE rates and associated symptoms, most likely due to a direct anti-viral activity. It is also possible that IFN- $\beta$  could modulate additional processes, such as

acting as an antagonist of Th2 immunity. Recent studies have shown that IFN- $\beta$  and type III IFN- $\lambda$  have potent Th2 antagonistic activity [28,29<sup>\*</sup>], suggesting that inhaled IFN- $\beta$  may deliver a benefit on two levels in atopic asthma, firstly reducing virus replication and hence virus driven inflammation, and secondly dampening the Th2 responses to allergens. Further studies with inhaled IFN- $\beta$  in AE are eagerly anticipated.

#### Macrolide antibiotics

Macrolides have been shown to have anti-inflammatory [30], bactericidal [31] and recently anti-viral activity [32<sup>\*</sup>]. The keto-macrolide telithromycin had previously shown efficacy in AE in adult asthmatics in a phase IV clinical trial [10]. The mechanism responsible for this beneficial effect is unknown, and telithromycin could have been merely acting as an anti-inflammatory agent. In cell based assays, azithromycin, but not the closely related erythromycin or telithromycin, was shown to have anti-viral activity to RV by inducing IFN and interferon stimulated genes (ISGs) [32<sup>\*</sup>]. This was a previously unknown property of azithromycin, and has since promoted the further investigation of azithromycin in phase IV clinical trials in AE which are currently ongoing.

#### Toll like receptor (TLR) 7/8 agonists

TLR7/8 recognise synthetic and virus encoded ssRNA and small analogues of nucleic acids including imiquimod, R848 and their derivatives. TLR7/8 are expressed on cells of myeloid or lymphoid origin including macrophages and DCs. While viruses certainly induce inflammation via recognition of ssRNA, the addition of TLR7/8 agonists in mouse models of allergen sensitisation and challenge [33,34<sup>\*</sup>] show a suppression of allergic airway inflammation. Why TLR7/8 agonists are protective in these models is not completely understood; however, it is generally accepted that TLR7/8 ligation may be useful in treating allergic diseases such as asthma. For example, recent studies of allergic airways inflammation following sensitisation and challenge to ovalbumin showed that the TLR7 agonist R848 was protective [33,34], reducing eosinophilic inflammation, lung function impairment and ovalbumin-specific Th2 T cell responses. Importantly, the effects of R848 were not observed in TLR7 deficient mice, showing that R848 acts as a TLR7 agonist and the protective effect is via TLR7 signalling [33].

#### Vaccines

The number of viruses implicated in the aetiology of asthma and their associated antigenic diversity has thus far limited development of effective vaccines.

There are a number of potential RSV vaccine candidates although none are currently licensed for use [35–38]. The creation of an effective RSV vaccine was significantly affected following the use of formalin inactivated RSV (FI-RSV) vaccine in the 1960s which led to increased

morbidity and enhanced respiratory disease following infection with live virus and the subsequent deaths of 2 children [39,40]. This phenomenon was felt to be as a result of induction of Th2 immune responses by the vaccine [41,42].

A new development in the creation of vaccines has been the use of TLR ligands as adjuvant agents. One recent study using monophosphoryl lipid A (MPLA), a derivative of bacterial LPS, incorporated with RSV virosomes demonstrated an enhanced Th1 response with increased production of IFN- $\gamma$  and decreased IL-5 in animals immunised with vaccine and then challenged with virus [36<sup>\*\*</sup>]. The MPLA adjuvanted vaccine conferred similar protection from live RSV virus as FI-RSV vaccine but with no evidence of enhanced respiratory disease. In addition the use of MPLA led to enhanced immunogenicity of the RSV vaccine with production of higher affinity antibodies.

The only vaccines commercially available and recommended for use are against influenza where the annual vaccine has been shown to play a key role in the prevention of virus infection and its associated morbidity [43<sup>\*</sup>]. This preventive approach may well have advantages over treatment of acute viral infections where current treatment options are limited.

As RV infections are implicated in the vast majority of virus induced AEs they are perhaps the most attractive target for a respiratory vaccine. However, there are >100 serotypes of RV and unlike influenza there is limited epidemiological information regarding the most important circulating serotypes [11<sup>\*\*</sup>]. Humans are infected with RV in early life and recurrently through life and most adults have antibodies to multiple RV strains, complicating human study of antibody responses. Improved diagnostic and molecular techniques have recently allowed the identification of the RV-C group further highlighting the difficulty in selecting specific serotypes for vaccine generation [11<sup>\*\*</sup>].

A major hurdle to the understanding of antibody production following virus infection has been a scarcity of animal models that have allowed us to study both asthma exacerbations and the subsequent effects of immunisation in greater detail [15]. A recent paper describing a novel mouse model of RV infection and immunisation has allowed study of RV mediated induction of antibody responses [44<sup>\*\*</sup>]. This paper demonstrated the generation of strong cross-serotype IgG responses to the RV capsid protein VP1 and that multiple infections were necessary to induce neutralising antibodies [44<sup>\*\*</sup>]. Another group have also recently shown that use of a recombinant VP1 protein was able to generate neutralising antibodies displaying cross-reactivity to distantly related RV strains [45]. These studies

suggest that efforts to develop RV vaccines may be worth re-visiting.

## Targeting the virus

### Small molecule inhibitors of virus infection and replication

Using small molecule inhibitors of RV infection, replication or release was a popular theme in the 1980s and 1990s for the treatment of the common cold. Despite approaches showing some promise in common cold studies, the use of these anti-virals has yet to be examined in virus induced AE. Small molecule anti-virals offer the advantages of being cost effective (small molecule production and validation), and their selectivity and safety is relatively straightforward to establish. They have disadvantages in that they may be limited to specific virus types, may select for escape mutants over time and may suffer from toxicity or have side effects with continual use.

The anti-RV agent Pleconaril was used in randomised, placebo-controlled, phase II clinical trials as a treatment of the common cold [46]. Pleconaril prevents uncoating of most serotypes of RVs. Pleconaril was tested as a therapeutic agent, with infected individuals beginning therapy 1–1.5 days after experiencing clinical colds. Pleconaril showed significant improvement in mean symptoms scores and decreases in mean duration of illness. Despite promising initial results, Pleconaril was abandoned as a treatment due to side effects.

The RV 3C protease inhibitor Rupintrivir was tested in a double blind, placebo-controlled phase II trial of experimental RV39 challenge [47]. Rupintrivir was designed to bind irreversibly to the RV 3C active site. As a prophylaxis, Rupintrivir reduced mean total symptom score, viral titre and nasal secretions but not the incidence or frequency of clinical colds. As a therapeutic treatment, Rupintrivir also reduced symptom scores, nasal secretions and viral titre.

The soluble ICAM derivative Tremacamra was tested in randomised double-blind placebo-controlled studies both as a therapeutic and prophylactic intervention to RV39 challenge [48]. Tremacamra showed promise as a therapy, reducing the frequency of colds, total symptom score, nasal mucus weight, and virus induced inflammation.

Quercetin is a polyphenol which has a range of properties some of which are anti-viral. Quercetin is thought to inhibit phospho-inositol-3-kinase inhibition and inhibition of viral endocytosis, RV and poliovirus protease activity, and RNA polymerase activity of some RNA viruses. In a mouse model of RV infection, Quercetin if given during infection reduced virus titre and improved lung function. However, if given daily for 10 days finishing 40 hours before RV infection, Quercetin had little effect on virus replication and lung function [49].

Development of all these drugs was abandoned for various reasons. However, considering the role of viruses in AE, and the available human and mouse models of virus induced AE, there has never been a better time to trial small molecule anti-virals as therapies for AE. The future is likely to witness further studies of anti-virals as a potential treatment for virus-induced AE.

### Virus specific antibodies

The recombinant monoclonal antibody (MAb) Palivizumab has been licenced for use in human RSV immunoprophylaxis since 1998 [50]. It acts against an epitope in the A region of the RSV fusion protein and has been shown to reduce the rate of hospitalisations in high risk-infants when used prophylactically [50]. There is a scarcity of evidence regarding the role of Palivizumab in the treatment of acute RSV disease with evidence predominantly limited to case reports and small retrospective studies. A single dose of 15 mg/kg in children intubated with respiratory failure due to RSV was shown to reduce RSV concentration in tracheal aspirates [50] and Palivizumab has been shown to be well tolerated in adult stem cell transplant recipients [51]. However, there is a need for further large scale studies to assess the role of Palivizumab as therapy in RSV infection.

Motavizumab (MEDI-524, MedImmune) is a second generation MAb developed from Palivizumab by affinity maturation [52]. In comparison to Palivizumab, it has been shown to bind to RSV F protein 70-fold better and have an approximately 20-fold improvement in neutralisation of RSV *in vitro* [52] as well as being able to reduce pulmonary RSV titres up to 100-fold lower than equivalent doses of Palivizumab [52]. Motavizumab is able to inhibit viral replication in the upper respiratory tract making it a potentially attractive therapy for treatment of RSV infection [52]. A study comparing Motavizumab with Palivizumab for RSV prophylaxis showed that Motavizumab treatment resulted in 50% fewer RSV related lower respiratory tract infections needing medical attention [53]. However, this study also documented an increase in cutaneous hypersensitivity reactions and Motavizumab is not currently licenced for use in humans.

There has been a growing body of work directed towards the generation of MAbs against influenza. Two recently described MAbs, Fi6v3 and PN-SIA28, have been shown to be broadly neutralising against both group 1 and 2 influenza A subtypes [54,55]. Fi6v3 antibody was generated from single cell culture of plasma cells from individuals following natural influenza A infection or vaccination and passive transfer of this MAb was protective in both mice and ferrets against H1, H3 and H5 subtypes [54]. PN-SIA28 was identified from a single healthy donor who had a negative history for influenza in the preceding decade and it too demonstrated neutralising activity against group 1 and 2 subtypes [55]. Both

Fi6v3 and PN-SIA28 act on regions near the HA stem and have identified new mechanisms underlying virus–host interaction and new areas of interest in development of anti-viral therapies [54\*\*,55\*\*]. There are currently no MAbS available for use against RV.

## Concluding remarks

Current treatment options for AE are limited and have developed little in recent years. Furthermore, these treatments do not address the cause of the exacerbations, nor specific mechanisms involved in their pathogenesis. New clinical studies are needed to further our understanding of the mechanisms of virus induced AE so that targets for development of novel approaches to prevention and therapy can be identified. Anti-viral therapies may be a source of these new therapies; this review has highlighted potential therapies that target the virus or boost host response to the virus. The latter approach is based on recent studies that show an impairment in the ability of the asthmatic host to raise an effective anti-viral immune response, and there are several potential ways to restore this. Alternatively, the virus itself may be targeted, using specific anti-virals or immunotherapy. We believe the future will likely see greatly increased study of anti-viral therapies in one form or another for treatment/prevention of virus induced AE.

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The authors describe a human monoclonal antibody able to neutralize pandemic influenza subtypes as well as other subtypes with pandemic potential.