Available online at www.sciencedirect.com

SciVerse ScienceDirect

Current Opinion in Pharmacology

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

Jaideep Dhariwal[1,2,3,4], Michael R Edwards[1,2,3] and Sebastian L Johnston[1,2,3,4]

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
[1] Airway Disease Infection Section, National Heart Lung Institute, Imperial College London, UK
[2] MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, UK
[3] Centre for Respiratory Infections, UK
[4] Imperial College Healthcare National Health Service Trust, London, UK

Corresponding author: Johnston, Sebastian L (s.johnston@imperial.ac.uk)

Current Opinion in Pharmacology 2013, **13**:331–336

This review comes from a themed issue on **Respiratory**

Edited by **Alastair G Stewart**

For a complete overview see the Issue and the Editorial

Available online 9th May 2013

1471-4892/$ – see front matter,

http://dx.doi.org/10.1016/j.coph.2013.04.010

Introduction

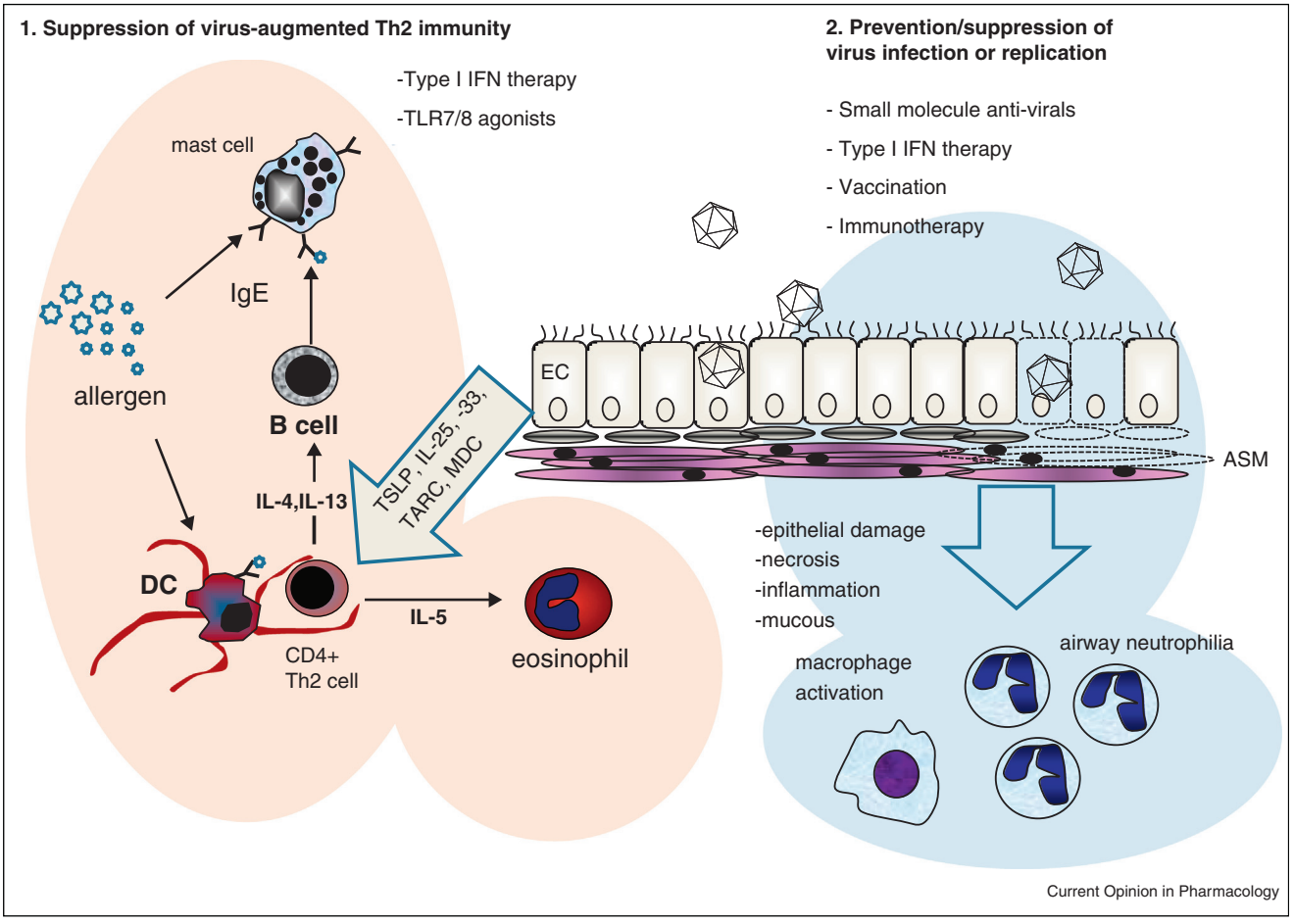
Asthma is a heterogeneous airway disease characterised by airway inflammation, airway hyperreactivity, reversible bronchoconstriction and airway remodelling. Patients experience shortness of breath, fluctuations in normal breathing patterns, and also periodic episodes of wheeze and cough. Asthma is treated 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, mucous 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••,16] and RV induced exacerbations of airway allergen challenge [15••,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-α, IFN-β or type III IFNs, the IFN-λs 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•,19,20••,21,22•,23,24••,25••,26••]. Importantly, deficient IFN-λ was also strongly related to virus load, and AE pathogenesis and severity *in vivo* [22•]. The mechanism responsible for impaired IFN-α, IFN-β and IFN-λ 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-β in poorly controlled adult atopic asthmatics was performed [27]. Inhaled IFN-β, 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-β improves AE rates and associated symptoms, most likely due to a direct anti-viral activity. It is also possible that IFN-β could modulate additional processes, such as