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ANTIVIRALS FOR VIRUS INDUCED EXACERBATIONS OF ASTHMA AND COPD TREATMENT

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ABSTRACT

Viral respiratory infections in patients with asthma or chronic obstructive pulmonary disease (COPD) can cause severe exacerbations, increasing the risk of secondary bacterial infections and having a significant impact on disease-related morbidity and mortality. Several antivirals such as oseltamivir and zanamivir evaluated in influenza and other virus-induced respiratory infections are discussed in this review as a starting point of their potential use in improving the outcome of asthma and COPD exacerbations. However, the efficacy of antiviral therapy for asthma/ COPD exacerbations needs a further evaluation.

Keywords: antiviral therapy, asthma, COPD, oseltamivir, zanamivir

Introduction

Chronic obstructive pulmonary disease (COPD) and bronchial asthma are both obstructive lung disease (OLD) with inflammatory pattern of the airways. Respiratory infections can be caused by viruses or bacteria and induced COPD or asthma exacerbations with steeply aggravated dyspnea and/or cough with sputum production, episodic bronchospasm and wheezing, mainly in smokers (1,2). Symptoms are, usually, controlled with inhaled corticosteroids and long-acting bronchodilators, which are able to reduce the airways inflammation and relieve the bronchospasm in a sustained manner (3). Viruses have been reported in ≥30% of exacerbations in COPD patients, respiratory syncytial virus (RSV), rhino-(RV) and influenza viruses (IV), being the most detected strains (4,5). In exacerbations of asthma, viral infections are commonly detected in children (6,7), especially, in unvaccinated ones (8).

The aim of this review consists in summarizing the existing data on the available antiviral therapies for the most common viruses involved in asthma and COPD exacerbations and discussing the potential indications.

1. Asthma and COPD with viral exacerbation: how to define the most appropriate target population requiring an antiviral therapy

In COPD patients, viral respiratory infections or combined viral-bacterial infection can have a significant impact on disease-related morbidity by determining more severe exacerbations (9-11). Rhinoviruses are the most prevalent viral strains isolated in COPD patients with severe respiratory symptoms and a longer duration of recovery after exacerbation (12). Chronic viral infection can "open the door" for chronic bacterial infections COPD-related, by interfering with endogenous bactericidal mechanisms (13). Persistent RSV infection of the airway epithelial cells can associated with an increased biofilm formation after culture co-incubation with Pseudomonas aeruginosa (14). The novel molecular diagnostic tests allow a better detection in revealing viral infections in asthma exacerbations reaching up a frequency to 80% (15). In both asthma and COPD exacerbations, rhino- and influenza viral infections are associated with a higher risk of frequent hospitalization (7,16,17). These data sustain the pathogenic role of chronic viral infection in asthmatics and COPD patients, highlighting the appropriateness and the effectiveness of antiviral therapies.

2. Antiviral therapy, a therapeutic approach in asthma/COPD exacerbators?

In influenza, AH1N1 pandemics, antivirals are most effective if promptly started, within the first 48 hours from the onset of disease (18). According to the type of viral strains, the severity of illness and the safety profile of the drug are different. Antiviral therapy is the earliest opportunity to reduce the risk of respiratory failure or death, especially, in hospitalized patients with progressive or complicated influenza.

Ribavirin is a nucleoside analogue, extensively used in patients with viral hepatitis C, children or lung transplant recipients with RSV infection (19), because it can interfere with viral strain multiplication. Its inhaled formulation was evaluated as safe in elderly patients with stable COPD (20).

M2 ion channel blockers (adamantanes): rimantadine and amantadine, currently, used as anti-Parkinson drugs, can inhibit the replication of influenza type A virus, have no effect on type B, poor safety profile, inducing rapid selection of resistance (21,22).

Neuraminidase inhibitors, more recently developed to treat and prevent influenza A and B, are represented by oseltamivir and zanamivir, widely, available, and perinamivir and laninamivir, with circumscribed availability.

Oseltamivir (Tamiflu®) is a prodrug activated, after liver passage, to oseltamivir carboxylate which inhibits the viral neuraminidase A, with consequent releasing of virions (23). Standard dosages of 75 mg/day or 150 mg/day showed efficacy in reducing the risk of pneumonia, illness severity and duration (24,25).

Zanamivir (Relenza®), used for prophylaxis or cure of influenza A and B infections, 5 days regimen of 10 mg inhaled twice daily, reveals an earlier reduction in symptoms score (26), lower risk of bronchitis in adults (27) and lower rate of bacterial complications requiring antibiotic use (28).

Peramivir (Rapivab®), a newer neuraminidase inhibitor, which inhibits the release of virions of influenza A and B, was, initially, developed as an oral formulation with a low bioavailability and, later, as a parenteral intravenous formulation given once daily, and tested, with efficacy, in critically ill patients (29,30).

Oseltamivir and **zaninamivir** were successfully used during AH1N1 pandemics.

Laninamivir is a long-acting neuraminidase inhibitor active against influenza A and B, including oseltamivir resistant strains, recently tested as inhaled formulation, delivered via dry powder, once daily, with efficacy analysis in 996 patients proving non-inferiority versus oseltamivir from the perspective of potential gastrointestinal side effects (31).

Other investigational compounds consist in new viral therapeutic targets (capsid structural proteins or C3 proteases), which allow the development of other antiviral therapies [pleconaril (capsid inhibitor) or rupintrivir (C3

protease inhibitor); RNA polymerase inhibitors, such as favipiravir], some of them still investigated for hepatitis C and Ebola virus, or authorized, in Japan, for influenza therapy (32,33). Monoclonal antibodies and interferons alpha, beta, gamma, lambda raised the interest as potential antiviral therapies for various respiratory infections (34,35).

Conclusion

In conclusion, the therapeutic role of antivirals in exacerbations of asthma/COPD is still unclear. There are limited data on the effectiveness in asthma/COPD exacerbations, insufficient knowledge of subset categories of illness, which could benefit of the antivirals addition to the conventional therapeutic recommendations, and lack of clear indications. The first problem can be solved by future clinical trials assessing of neuraminidase inhibitors or monoclonal antibodies in COPD viral exacerbations as curative therapies. Antiviral therapy can improve outcomes of OLD exacerbations such as reduced mortality risk, reduced intensive care unit (ICU) and/or hospital admission, reduced in hospital respiratory failure risk, and the last, but not the least, reduced hospitalization duration. The impact of viral infections on COPD exacerbation is more important than on asthma exacerbation. It is not clear if antivirals can be universally indicated in any asthma/COPD exacerbations. An important step ahead would be the identification of a reliable biomarker of impaired innate immunity in patients with frequent exacerbations. Although viral infections can increased the OLD morbidity and mortality, current guidelines are focused more on preventing influenza than treating.

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