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REVIEW

Toward antiviral therapy/prophylaxis for rhinovirus-induced exacerbations of chronic obstructive pulmonary disease: challenges, opportunities, and strategies

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SUMMARY

Chronic obstructive pulmonary disease (COPD) is a life-threatening lung illness characterized by persistent and progressive airflow limitation. Exacerbations of COPD contribute to the severity of this pathology and accelerate disease progression. To date, pharmacological treatment of both stable COPD patients and patients experiencing exacerbations is mainly symptomatic with bronchodilators and steroids as the mainstay of therapy. Bacteria trigger such exacerbations in a number of cases; hence, antibiotics might be included in the treatment as well. Several respiratory viruses are frequently detected in sputum from patients during COPD exacerbations. These include influenza viruses, respiratory syncytial virus, and, most often, rhinoviruses. In this review, we discuss the potential use of an anti-rhinovirus drug for the treatment and prophylaxis of rhinovirus-induced COPD exacerbations and the path forward toward the development and use of such a drug. Copyright © 2015 John Wiley & Sons, Ltd.

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ACUTE EXACERBATIONS

According to the most recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) report (2015), COPD is defined as a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [1].

Typical symptoms of COPD include chronic and progressive dyspnea, cough, and sputum production. Exacerbations (acute deteriorations of symptoms and lung function) and comorbidities (e.g. cardiovascular diseases, osteoporosis, depression, and lung cancer) contribute to the severity of the illness. Forecasts of the World Health Organization state that by 2030, COPD will be the fourth leading cause of death worldwide [2]. In 2007, the international burden of lung disease study, based on a population of adults above 40 years old, estimated global prevalence of moderate to very severe COPD at 10%, with a substantial difference between continents based on the presence of risk factors [3]. COPD seems more prevalent in current or past smokers, persons over 40 years of age, and men [1,3]. The multifactorial etiology of COPD depends on genetic predisposition as well as exposure to risk factors, such as cigarette smoking, occupational exposure (e.g. dusts, chemical agents, and fumes), and indoor air pollution [1,4]. Following exposure of the lungs to such noxious agents, an

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Abbreviations used

AE, acute exacerbation; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; HRV, human rhinoviruses; NIs, neuraminidase inhibitors.

abnormal inflammatory response is triggered that results in parenchymal damage and in remodeling of the small airway compartment, eventually leading to progressive airflow limitation [4]. Clinical diagnosis of COPD is based on spirometry: Persistent airflow limitation is confirmed with a post-bronchodilator value of the forced expiratory volume in 1 s (FEV_1) divided by the forced vital capacity of less than 0.7 [1]. According to the severity of airflow limitation, COPD patients with a post-bronchodilator FEV_1/forced vital capacity < 0.7 are often classified in GOLD grades 1–4 (Table 1). Effective disease management of stable COPD not only consists of a reduction of the patient's symptoms (pharmacological treatment) but also includes identification and reduction of exposure to risk factors (non-pharmacological treatment, e.g. smoking cessation) together with pulmonary rehabilitation [1,4]. Bronchodilatation with long-acting ß2-agonists and/or long-acting anticholinergics as a maintenance regimen forms the core [1]. For patients at high risk of exacerbations, inhaled corticosteroids can be added to the treatment. To prevent infections resulting in a deterioration to severe exacerbations, all COPD patients are recommended to receive influenza and pneumococcal polysaccharide vaccinations [1].

The stable course of a COPD patient can be abruptly interrupted by an acute exacerbation (AE-COPD), which is defined as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication" [1]. Alternatively, more strict definitions of AE-COPD are based on "major" and "minor" symptoms, where major symptoms include a change in sputum purulence, increased dyspnea, and increased sputum amount, whereas increased nasal discharge/congestion, wheezing, sore throat, and cough are classified as minor symptoms ("Anthonisen criteria") [5,6]. Using these parameters, exacerbations are then defined as an increase in any two major symptoms or an increase in one major and one minor symptom, during two consecutive days. Consequently, the current exacerbation diagnosis is solely based on the clinical presentation of the patient. The frequency of exacerbations increases together with the severity of COPD [7]. Moreover, exacerbation frequencies show a positive correlation with older age, a lower body mass index, lower FEV_1 (in per cent of predicted value), and a history of prior exacerbations [7,8]. As some patients are more prone to exacerbations than others, the most reliable parameter to predict future exacerbations across all GOLD grades seems to be the history of prior exacerbations [7]. Furthermore, in the northern and southern hemispheres, exacerbations have a seasonal pattern as they are more prevalent during winters, whereas in the tropics, no seasonality is observed [8]. Several factors can trigger an AE of COPD, including air pollution, pneumonia, congestive heart failure, and interruption of maintenance treatment. Among the most well-recognized triggers, however, are respiratory infections [9]. Despite this knowledge, the specific trigger remains undetermined in about one third of the severe cases [1,4]. The management of an AE-COPD should reduce the clinical impact of the current exacerbation on the patient as well as prevent future exacerbations. Currently, primary treatment of AE-COPD consists of increasing the dose or frequency of a short-acting beta 2-agonist with or without a short-acting anticholinergic [1]. In a subsequent step, oral corticosteroids are added [1]. Antibiotics can be considered if there are signs of a bacterial infection, such as purulent sputum or when the patient presents with three major symptoms, as described earlier [1,10]. The initial empirical antibiotic treatment usually consists of an aminopenicillin with or without clavulanic acid, a macrolide, or a tetracycline. However, the local bacterial resistance pattern and the patient's exacerbation history should be considered when selecting an antibiotic [1]. With the exception of the use of antibiotics, therapy of AEs thus remains merely symptomatic. The identification of specific etiologies that serve as triggers for an AE-COPD should

Table 1. Classification of chronic obstructive pulmonary disease patients into different Global Initiative for Chronic Obstructive Lung Disease grades 1–4

FEV_1	Grade
≥80% predicted	Grade 1 (mild)
50% ≤ FEV_1 < 80% predicted	Grade 2 (moderate)
30% ≤ FEV_1 < 50% predicted	Grade 3 (severe)
FEV_1 < 30% predicted	Grade 4 (very severe)

FEV_1, forced expiratory volume in 1 s.

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allow a more rational and targeted therapy to reduce the severity and prevalence of COPD exacerbations.

RESPIRATORY INFECTIONS AS A TRIGGER FOR ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Respiratory infections are one of the factors that are well recognized to trigger an AE of COPD. The role of certain bacteria, including *Haemophilus influenza*, *Streptococcus pneumonia*, and *Moraxella catarrhalis*, is well established, and their presence forms the justification for the empirical treatment with antibiotics during an exacerbation [11]. On the other hand, the role of viruses in AE-COPD has been much less well recognized and understood [12–17]. With the use of sensitive diagnostic techniques, such as RT-PCR, more and more studies report on the presence of viruses during AE-COPD. Respiratory viruses have been observed in sputum or nasal swabs during AE-COPDs in 22–64% of all cases. The most commonly detected viruses in AE-COPD are human rhinoviruses (HRV, 3–27%), influenza virus A (2–36%), influenza virus B (2–6%), parainfluenza virus 3 (0.6–7%), coronaviruses (1–9%), adenovirus (0.6–7%), human metapneumovirus (1–8%), and RSV (0.7–41%) (Figure 1) [6,13–28]. In other studies, influenza B virus and RSV were not detected [19,22]. Apart from their presence in samples obtained during exacerbations, both bacteria and viruses have as well been detected in patients with stable COPD (Figure 1) [6,19–21]. Nonetheless, viruses are detected at a greater frequency during AE-COPD than during stable COPD, with the exception of RSV for which conflicting results have been observed in patients with stable COPD

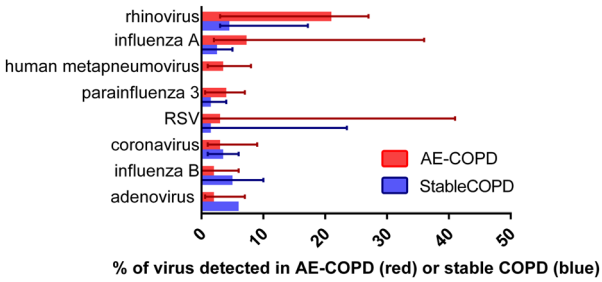

Figure 1. Viral pathogens during acute exacerbations [6,13–28] and stable chronic obstructive pulmonary disease (COPD) [6,19–21]. For each virus, the median and the range of the reported detection levels of viral RNA during acute exacerbation of COPD (red) and stable COPD (blue) are shown

[2,6,20,21,25,28–31]. Differences in sample origin (e.g. sputum versus nasal lavage), duration between the onset of the exacerbation and the sampling, and the detection method (e.g. serology or PCR, and sensitivity of the PCR) are a few among many parameters that can explain the large variability between different studies. Furthermore, low influenza vaccination rates or infections with influenza strains that are not included in the vaccine used during that particular season may account for the high detection levels of influenza virus in some studies [17]. Altogether, in the majority of the studies, rhinoviruses appear to be the most frequently detected viral pathogens during AE-COPD regardless of the variability.

Rhinoviruses are single-stranded (+) RNA viruses that belong to the family *Picornaviridae*. Currently, more than 150 rhinovirus strains, which are divided into three species, HRV-A, HRV-B, and HRV-C, have been identified. The HRV-C types (to date 51 strains) have only recently been discovered with the advent of RT-PCR and genome sequencing techniques, as culturing of these viruses has appeared to be notoriously difficult [32,33]. For a long time, rhinoviruses were considered as "harmless" viruses, causing only a mild upper respiratory infection, referred to as the "common cold." However, during the latest decades, the presence of rhinoviruses was observed not only in the upper respiratory tract but also in the lower respiratory tract [34], more specifically in patients suffering from AE-COPD [6,15,16,18–23,25–27]. Despite this discovery, the role of viruses as an etiology of AE-COPD remained a matter of debate. Indeed, the presence of virus during AE-COPD does not necessarily imply a causative link between an ongoing infection and a COPD exacerbation. Recently, however, an experimental rhinovirus infection study in COPD patients provided the first evidence of a causal relationship between rhinovirus infections and AE-COPD [35,36]. In this study, both non-COPD smokers and COPD patients developed upper and lower respiratory symptoms following an experimental rhinovirus infection. Lower respiratory symptoms were more severe and prolonged in COPD patients than those in the control subjects. In COPD patients, respiratory symptoms following HRV infection met the criteria of a mild, self-limiting AE with upper respiratory symptoms peaking at day 3 and lower respiratory symptoms peaking at day 9. The viral load was elevated from

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day 1 to day 15, with peak viral load at days 4–8 in nasal lavage and day 5 in sputum [35,36].

Apart from single viral or bacterial infections, co-infections (virus/virus or virus/bacteria) have been reported in 7–25% of all COPD exacerbations [13,16,18,21,23,24,26,27]. It is currently still unclear how these dual infections contribute to the clinical severity of AE-COPD because conflicting outcomes have been reported over the years [16,21,25,37]. In an experimental rhinovirus infection study, secondary bacterial infections following rhinovirus infection were observed in 60% of the COPD patients and in only 10% of the smoking and non-smoking control subjects [37]. Furthermore, analysis of the lower airway microbiome prior to and following experimental rhinovirus infection in COPD patients revealed an outgrowth of pathogenic bacteria such as *H. influenza* from the existing microbiota following infection [38]. Consistent with this experimental model, George and colleagues provided further evidence for a direct link between initial HRV infection and secondary bacterial outgrowth [28]. These observations suggest that viral infections might facilitate subsequent secondary bacterial infection. In contrast to influenza viruses, which cause massive cell death of epithelial cells, it is less clear whether rhinoviruses do the same [39]. Several other *in vitro* mechanisms by which rhinovirus infections may predispose the host to secondary bacterial infections have been proposed [40–42].

Thus, the role of respiratory viruses in general and that of rhinoviruses in particular, during acute COPD exacerbations, is becoming increasingly apparent. The following observations support a role for respiratory viruses in AE-COPD: the high levels of viral RNA/DNA during AE-COPD in sputum samples, the observation that common cold symptoms often precede AE-COPD [6,43], and the seasonality of AE-COPD, which coincides with the seasonality of respiratory viral infections [8]. Despite the small sample size, the experimental infection study by Mallia and colleagues [36] can be considered as a milestone in the demonstration of a causal link between the two events. The existence of such causal link may have major clinical implications when considering the management of COPD patients that present with an AE. Indeed, if it were possible to detect and define the COPD patients in which an AE is triggered by a rhinovirus infection, potent anti-rhinovirus drugs could complement the current pharmacological armamentarium. Before such strategies can be implemented, several questions need to be addressed.

TOWARD POTENT AND PAN-SEROTYPE ANTI-RHINOVIRUS AGENTS

To combat viral infections, two major strategies are generally recognized: a prophylactic approach by means of vaccination/immunoprophylaxis and a therapeutic approach typically using small molecule inhibitors. For influenza, vaccination is recommended for all COPD patients, and observational studies clearly confirm the benefit of such strategy (Figure 2) [1,17]. In the case of RSV, passive immunoprophylaxis with palivizumab (Synagis, MedImmune, Gaithersburg, Maryland, USA), a humanized monoclonal antibody, is being used in premature high-risk infants [44]. The use of palivizumab in the elderly or in COPD patients has not been assessed so far (Figure 2). Because of the large number of different HRV types and antigenic heterogeneity, the development of a rhinovirus vaccine appears to be extremely difficult as illustrated by several failed attempts [45,46]. The use of highly potent antivirals, on the other hand, offers a more realistic strategy to reduce the burden of rhinovirus infections in COPD patients. Such an antiviral drug should ideally possess broad-spectrum activity against all members within the large group of rhinoviruses. In the 1980s and 1990s (which was before the role of rhinoviruses in COPD exacerbations was recognized), a number of pharmaceutical companies had programs to develop rhinovirus inhibitors for the treatment of common cold infections [47]. However, none of these

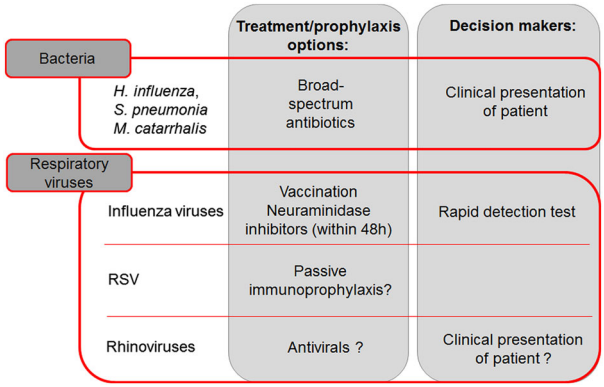

Figure 2. Microbial involvement in chronic obstructive pulmonary disease exacerbations and (necessary) therapeutic interventions

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compounds developed was eventually approved for human use. So far, the most widely explored drug target for inhibition of rhinovirus replication has been the viral capsid (Figure 3). The so-called capsid binders exhibit their antiviral action by targeting the attachment/entry/uncoating process of the virus [48]. In 2002, a new drug application for the capsid binder pleconaril (WIN63843, Schering-Plough, Kenilworth, New Jersey, USA) for the treatment of common colds was rejected by the Food and Drug Administration, mainly because of safety concerns [49]. Currently, another capsid binder, designated vapendavir (BTA798, an analog of pirodavir, Biota Holdings, Alpharetta, Georgia, USA), is in clinical development to treat rhinovirus-induced exacerbations of asthma [50,51]. In 2009, a clinical proof of concept was obtained in an experimental rhinovirus infection study with healthy volunteers: 9-day oral treatment with 400 mg vapendavir twice a day (2 days prior to infection) significantly reduced viral load [52]. In March 2012, Biota successfully completed a phase II multicenter, randomized, double-blind, placebo-controlled study in mild asthmatic adults with symptomatic, naturally acquired rhinovirus infection. After 3 days of treatment, severity of the cold symptoms (Wisconsin Upper Respiratory Symptom Survey-21) was significantly different between vapendavir treatment and placebo (based on nonpeer-reviewed data; NCT01175226, URL: www.clinicaltrials.gov). In a March 2015 press release, Biota announced the commencement of a phase IIb multicenter, randomized, double-blind, placebo-controlled dose-ranging study in laboratory-confirmed HRV-infected patients with moderate-to-severe asthma (referred to as the SPIRITUS trial) [53]. Additional studies confirming the efficacy of vapendavir for the treatment/prevention of COPD exacerbations with natural rhinovirus infections in phase II trials are awaited.

The 3C protease, responsible for the processing of viral proteins, is another well-studied drug target in the rhinovirus replication cycle (Figure 3). Despite potent *in vitro* activity against a broad panel of rhinovirus strains, the 3C protease inhibitor rupintrivir (AG7088, Pfizer) (a compound with low oral bioavailability) proved not to be effective in natural rhinovirus infection studies, and its development and that of an analog with better oral bioavailability were therefore halted [54,55].

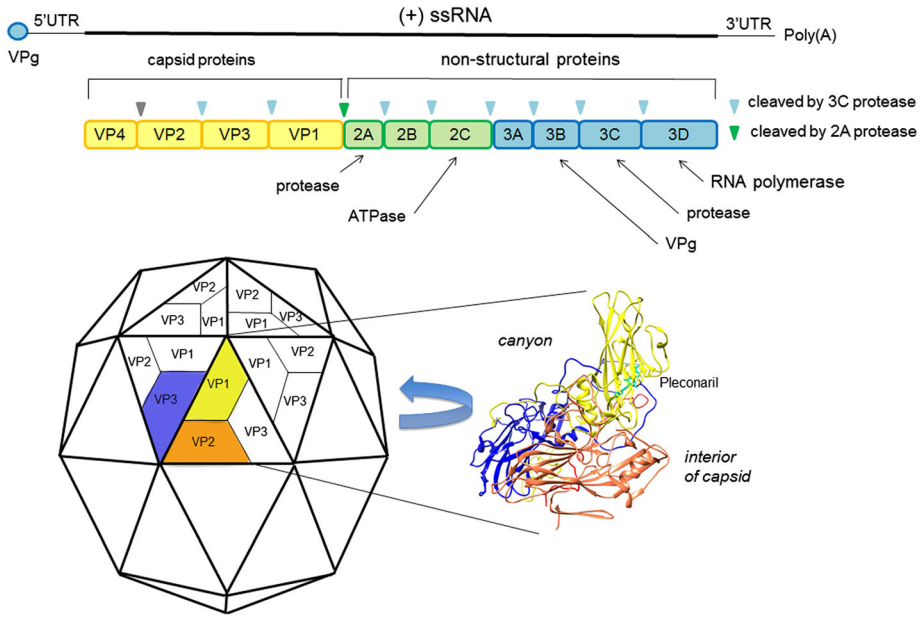

Figure 3. Organization of the rhinovirus genome and polyprotein. The single-stranded RNA genome encodes for four structural proteins {consisting of viral protein [VP1–4] and seven non-structural proteins [comprising two proteases (2A and 3C), one polymerase (3D), one putative ring helicase/ATPase (2C), VPg, and two other proteins that, either cleaved or as a precursor, are involved in viral replication]}. The icosahedral virion consists of 60 monomers, and one monomer consists of four structural proteins VP1 (yellow), VP2 (orange), VP3 (blue), and VP4 (inside of the particle). On the right, an enlarged monomer is depicted (Protein Data Bank (PDB) file 1NCQ) [82]. Pleconaril (cyan) interacts with a hydrophobic pocket beneath the canyon

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Development of drug resistance is a major issue during the treatment of chronic viral infections such as those caused by HIV and HCV. The development of combinations of drugs with non-overlapping resistance profiles has been key in avoiding resistance development during long-term treatment of chronic viral infections [56,57]. The most recent combinations of HCV drugs (in development or very recently appeared) consist of one well-tolerated pill a day for 8–12 weeks and result in >95% cure (sustained virological response) [56] of once daily therapy with potent antivirals. Rhinoviruses cause, unlike HIV and HCV, merely acute infections. Hence, much shorter treatment regimens, which should also largely reduce the risk of resistance development, may be needed. However, rhinoviruses have, like most RNA viruses, a high mutation rate [58]. During phase II clinical trials with the capsid binder pleconaril, virus variants with reduced susceptibility or even full resistance were detected in, respectively, 11% and 3% of the drug-treated subjects [59]. All capsid binders, including vapendavir and pleconaril, share the same target, selected readily for resistance, and drug-resistant variants are, at least in cell culture, cross resistant [51]. Furthermore, several studies suggest that RV-C species might have an inherent resistance to capsid-binding agents [60,61]. Therefore, novel anti-rhinovirus drugs should ideally have a high barrier toward drug resistance, and drugs with non-overlapping resistance profiles may be needed [62]. The picornavirus genome encodes several other potential targets for inhibition of viral replication. We identified not only highly potent inhibitors that target the 2C protein (an NTPase and putative ring helicase) [63] and the RNA-dependent RNA polymerase [64] but also a class of compounds that targets VP4, a capsid protein involved in the release of viral RNA from the capsid (our unpublished data) (Figure 3).

Thus, besides studies that explore the use of capsid binders and earlier work on the viral 3C protease, very few events/proteins in the rhinovirus replication cycle have been explored as potential targets for inhibition of viral replication. In analogy to other viruses (herpesviruses, HBV, HIV, and HCV), it may well be possible to design polymerase inhibitors. Yet other viral proteins may form excellent targets for inhibition of viral replication. Potent and safe antiviral drugs are successfully being used for the treatment of a number of other viral infections; it should hence be very well achievable to develop a safe pan-rhinovirus inhibitor ideally with a high barrier to resistance.

WHAT PHARMACEUTICAL AND CLINICAL PROPERTIES SHOULD A DRUG TO TREAT RHINOVIRUS-INDUCED ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE POSSESS?

A pharmaceutical formulation for inhaled delivery (with breath-actuated devices) may be preferred as it limits systemic side effects and provides the drug directly to the target site [65]. Easy manipulation of the dosage form by the patient, preferentially in a once or twice daily dose, is essential for optimal adherence. An anti-rhinovirus drug should delay or reduce the upper respiratory tract symptoms so that a potential antiviral effect can be relatively easily monitored in healthy volunteers who are experimentally infected with a rhinovirus (as was recently demonstrated for the capsid binder vapendavir in a proof-of-concept study) [52]. Once effectiveness in experimentally infected healthy individuals has been shown, efficacy trials may be conducted in COPD patients with naturally occurring infections. Besides symptom scoring, the effect of treatment with an anti-rhinovirus drug on lung function and sputum production should be monitored as well as the duration and frequency of exacerbations. Virological measurements (e.g. virus shedding) should be quantified as secondary endpoints [66]. To that end, standardized sampling and detection methods should be established. The effect of smoking, vaccination against influenza, and the use of co-medication such as bronchodilators, steroids, and antibiotics should be taken into account during the evaluation of the efficacy of the drugs [67]. Such a trial should be conducted over 1 year to prevent seasonal bias. Phase IIa trials with drugs to be used for the treatment of COPD are typically focused on grade 2 COPD patients (>35 years, including geriatric patients, with spirometric documented COPD and no asthma). Efficacy in grade 3 and 4 patients with severe AE-COPD (e.g. requiring hospitalization) should ideally be assessed as well [65,67]. These latter patients would probably benefit most from treatment, provided that exacerbation frequency is higher in grade 3 and 4 patients [7]. So far, no clinical trials with anti-rhinovirus drugs have been conducted in COPD patients. Clinical

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trials with pleconaril and rupintrivir as therapies for common colds focused solely on upper respiratory symptoms (such as sneezing, nasal obstruction/congestion, and cough) and viral load reduction in otherwise healthy individuals [68,69]. Vapendavir has been shown to reduce the severity of common cold symptoms in asthma patients after a naturally occurring rhinovirus infection (nonpeer-reviewed data; NCT01175226, URL: www.clinicaltrials.gov). Vapendavir treatment also had a beneficial effect on lung function and the use of asthma reliever medication as compared with control. These data suggest that vapendavir, and thus likely also more potent antiviral drugs, may result in a beneficial effect not only in asthmatic but also in COPD patients.

WHICH PATIENTS WOULD BENEFIT FROM ANTI-RHINOVIRUS THERAPY AND WHEN?

Whether anti-rhinovirus drugs can be successfully employed in the treatment of COPD exacerbations depends not only on the potency of the drug but also on the time frame between the onset of illness and the initiation of the treatment (Figure 4). Rhinoviruses, akin to influenza viruses, cause acute infections, characterized by a transient viral replication that elicits an inflammatory response. Following experimental influenza infection in healthy subjects, peak viral load and peak scores for systemic symptoms (fever) coincide at day 2 post-infection, while respiratory and nasal symptoms peak at day 3 [70]. Symptom relief of an influenza infection following treatment with neuraminidase inhibitors (NIs) illustrates the feasibility of an antiviral intervention in an acute respiratory infection [71,72]. In influenza-infected asthma or COPD patients that received treatment with the NI zanamivir, the median time to alleviation of symptoms was shortened by 1.5 days [73]. To be effective, treatment with an NI should be initiated within 48 h after the onset of fever [74]. Experimental rhinovirus infections in healthy volunteers resulted in a peak of viral replication and upper respiratory tract symptoms that coincided 2–4 days after infection [36,58]. However, as discussed earlier, in an experimental infection study in COPD patients, upper respiratory symptoms preceded lower respiratory symptoms and peak viral load with approximately 1 day [36]. Such symptom progression from upper to lower respiratory tracts is also observed in naturally occurring exacerbations:

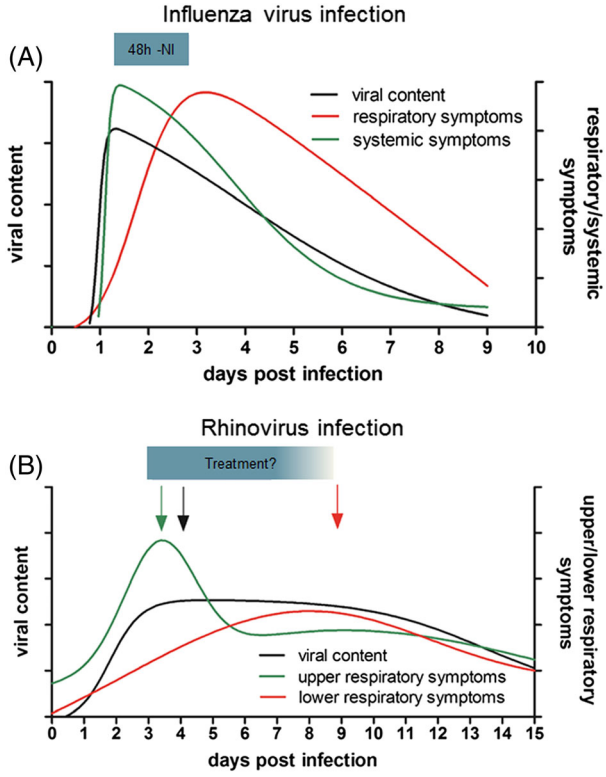

Figure 4. Simplified scheme of an experimental influenza and rhinovirus infection. (A) Following experimental influenza infection in a healthy individual, viral RNA load (black) increased from day 1, peaked at day 2, and returned to baseline at day 8. Systemic symptoms (green) peaked at day 2 and resolved faster than the respiratory symptoms (red, peak at day 3). Treatment with neuraminidase inhibitors is recommended to start within 48 h after fever onset. Figure based on data from reference [71]. (B) Rhinovirus infection of a chronic obstructive pulmonary disease patient resulted in a fast increase in upper respiratory tract symptoms (green, peak at day 3) and a slower and more prolonged increase in lower respiratory tract symptoms (red, peak at day 9). Viral RNA load (black) peaked at day 4 post-infection. Blue box: suggested period of therapy initiation with an anti-rhinovirus drug. Figure based on data from reference [36]

29–64% of all exacerbations were associated with common cold symptoms [6,43], and when associated with a cold, the upper respiratory symptoms preceded the exacerbation in 84% of the cases [43]. Therefore, in the case of a rhinovirus infection, the patient would present with upper respiratory symptoms, which may be used as reference symptoms to initiate treatment (as is fever onset for influenza treatment). Notwithstanding the limited data in COPD patients and the need for more research, the available evidence supports the idea that common cold symptoms precede the actual

exacerbation, which in turn creates a time frame to initiate antiviral treatment and prevent deterioration toward an AE-COPD.

Another question that needs to be addressed is whether or not it is necessary to confirm the presence of rhinoviruses prior to the initiation of therapy. For AE-COPD triggered by a bacterial infection, typing of bacteria is usually not performed because broad-spectrum antibiotics are available, covering most of the bacteria involved in exacerbations (Figure 2) [75]. In contrast, a genetically diverse group of respiratory viruses such as rhinoviruses, influenza viruses, RSV, parainfluenza, and adenoviruses is associated with AE-COPD. The development of a broad-spectrum antiviral drug targeting all these viruses [including (−) ssRNA, (+) ssRNA, and dsDNA viruses] is for several reasons that we will not address in this review, not likely. Treatment with an anti-HRV drug should ideally only be initiated following confirmation of an HRV infection, to avoid the irrational use of medication. For infections with an influenza virus, rapid diagnostic immunoassays (based on the presence of the nucleoprotein antigens) are available, and these tests can be completed in a clinically relevant time frame (e.g. 15 min) (Figure 2) [76]. However, such "point-of-care" diagnostic assays do not yet exist for rhinoviruses. The development of successful anti-rhinovirus drugs may be the required incentive to develop such rapid diagnostic assays for rhinovirus infections. The current detection methods (serology, culturing of the virus, or RT-PCR) are not relevant in a clinical diagnostic setting, because they require specialized devices, are time consuming and expensive, or lack specificity. Confirmation of a rhinovirus infection using these methods would delay the onset of treatment in such a way that the therapeutic benefit of the intervention would be lost. Currently, initiation of antiviral treatment within a relevant time frame is only possible if it is based on the clinical presentation of the patient, akin to what is currently performed for antibiotic treatment.

Besides therapeutic treatment, another possible strategy in high-risk COPD patients is prophylaxis in a household or community setting. Most acute respiratory infections, including influenza and RSV, cause seasonal epidemics during 2–4 months, and seasonal prophylaxis would be an option to prevent such infections [77,78]. Drug compliance during seasonal prophylaxis may not be easily achieved in some patients, and the rather low degree of seasonality of rhinovirus infection [79] together with the possibility of resistance development toward the drugs with a low barrier to resistance (such as capsid binders) disfavors prophylactic use. Household prophylaxis of high-risk COPD patients when a household member presents with common cold symptoms may be important to explore. For influenza, it has been shown that the NI zanamivir markedly reduced, when used prophylactically, the chance of household symptomatic infections [80]. The duration of the prophylaxis will depend on the length of rhinovirus shedding from the index case. For rhinoviruses, viral load in nasal lavage and sputum was elevated for 15 days following experimental infection [36]. Virus shedding following an influenza infection has a mean duration of 5 days while antiviral prophylaxis in a household setting is recommended for 10 days [80,81].

CONCLUSIONS

Today, the global health burden of COPD is well recognized, and one of the main aims of COPD treatment is to reduce the number and severity of AEs. The current therapeutic strategy for such exacerbations consists of the use of bronchodilators and inhaled steroids and remains mainly symptomatic. There is now a preponderance of evidence for a prominent role of respiratory viruses such as rhinoviruses, influenza, and RSV in AEs of COPD. The causal role of viruses, in particular rhinoviruses, as a trigger of COPD exacerbations has recently been demonstrated in experimentally infected patients. It can therefore be anticipated that antiviral therapy may lower the burden of virus-induced COPD exacerbations. Anti-(rhino)virus inhibitors have so far never been evaluated for the treatment of COPD exacerbations. To this end, potent and safe inhibitors of rhinovirus replication with pan-serotype coverage should be developed. Certain capsid binders (pleconaril and vapendavir) exert such potent activity but lack activity against some serotypes and may readily select for resistance (or have at least been shown *in vitro* to do so). Given the fact that viral protease inhibitors are highly efficient in the treatment of HIV and HCV (both chronic) infections, it is reasonable to assume that rhinovirus protease inhibitors may have their role in the treatment of rhinovirus infections. The picornavirus genome encodes several other potential

targets for antiviral drugs, among which are the 2C protein (an NTPase and putative helicase) and the 3D RNA-dependent RNA polymerase. Highly potent polymerase inhibitors (either nucleoside or non-nucleoside analogs) are being used for the successful treatment of infections with herpesviruses, HIV, and the hepatitis B and C viruses; also for this target, it may be very well possible to develop highly potent inhibitors that efficiently control rhinovirus infection. A proof of concept that treatment with a rhinovirus inhibitor may result in a clinical beneficial effect on rhinovirus-induced asthma exacerbations was recently reported using the capsid binder vapendavir. A drug that is to be used to stop rhinovirus replication will likely require an early initiation of treatment. For the influenza NIs, it has been shown that treatment should be initiated during the first 48 h after onset of symptoms to obtain a clinical effect. In an experimental rhinovirus infection study in a small group of COPD patients, upper respiratory symptoms preceded lower respiratory symptoms and peak viral load by approximately 1 day. More data are required about the time course of these different symptoms in COPD patients; nonetheless, this evidence is in line with the observations that common cold symptoms precede the exacerbation. This time course creates an opportunity to initiate antiviral treatment and prevent deterioration toward severe exacerbations. Symptoms of a common cold can be relatively well recognized by a patient. It may hence be expected that a majority of the COPD patients may recognize such symptoms and feel motivated to initiate therapy. For clinical trials with rhinovirus inhibitors but more importantly to treat the correct subpopulation of patients, it might be advisable to develop easy and rapid diagnostic tools. Seasonal prophylaxis may be complicated by the fact that rhinovirus infections show a less clear seasonal pattern than influenza virus infections. Household prophylaxis of high-risk COPD patients for the prevention of rhinovirus-induced exacerbations of COPD should be explored.

In conclusion, today, highly potent and safe drugs are available for the treatment of infections with herpesviruses, HIV, HBV, HCV, and, to a lesser extent, influenza viruses. The rhinovirus genome encodes several good targets for therapy; it should hence be very well possible to develop highly potent, safe, and broad-spectrum anti-rhinovirus drugs with a high barrier to resistance. Such drugs may have an important place in the prevention and/or reduction of the severity (either as prophylaxis or as treatment) of rhinovirus-induced exacerbations of COPD.

CONFLICT OF INTEREST

The authors have no competing interest.

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