

# Novel Antiviral Agents for Respiratory Viral Infection in Immunocompromised Adults

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**Abstract** Respiratory viruses cause significant morbidity and mortality in immunocompromised populations such as stem cell transplant and solid organ transplant patients. Few viruses causing respiratory tract infection have an approved therapy, and many of the viruses have no therapeutic options at all. In this article, we describe novel agents under development for treatment options against several respiratory viruses.

**Keywords** Respiratory viruses · Immunocompromised · Therapy

## Introduction

Respiratory viruses cause a wide range of upper and lower respiratory tract infections (URTIs and LRTIs) in the general population. In the immunocompromised populations, particularly those undergoing chemotherapy for malignancy and solid organ and hematopoietic stem cell transplant patients, viral respiratory infections can cause high rates of morbidity and mortality. Few antiviral therapies exist that provide benefit against these pathogens, but new therapies are under investigation [1, 2]. However, there remain limited data about the efficacy of many of these new agents in immunocompromised populations. This review describes the currently published literature regarding novel antiviral agents for use against respiratory viruses in the immunocompromised host.

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## Influenza

Influenza, a single-strand, segmented RNA virus, remains one of the more challenging respiratory viral infections for the immunocompromised population. The mainstay of treatment for seasonal influenza, pandemic H1N1, and influenza B continues to be the neuraminidase inhibitors (NAIs) oseltamivir and zanamivir; although the M2 inhibitors amantadine and rimantadine are approved for influenza A, widespread resistance at present precludes use of the latter class of agents [3]. One limitation to the use of NAIs is the emergence of resistance, which occurs more frequently in immunocompromised populations [4].

## Peramivir

Peramivir, an intravenous (IV) NAI, has been studied for the treatment of more severe influenza infections. Peramivir use emerged under the Emergency Investigational New Drug (eIND) program in 2009 to treat serious illness caused by pandemic influenza A H1N1. In one review of patients from 18 different states, only 3 of 31 (9 %) patients treated under eIND during the early phase of the pandemic were transplant patients: 2 patients with solid organ transplants and 1 with hematopoietic stem cell transplant (HSCT) [5]. An additional 5 patients in the eIND cohort were on systemic corticosteroids. Overall, the authors classified 7 patients who received peramivir as immunocompromised, of which 2 were children. All of the patients in the study had severe illness with respiratory failure. Two adult patients died, while 3 recovered. One child recovered, and 1 died with peramivir therapy.

In a review of peramivir use under the emergency use authorization in California, the authors identified 12 immunosuppressed patients (21 % of the total), defined as “immunosuppressive drugs, cancer, chemotherapy, leukemia, systemic lupus erythematosus, transplant, or other immunosuppressive conditions” [6]. Five of 12 patients lived; baseline

characteristics did not predict mortality in this cohort. Finally, several case reports describe treatment with peramivir. In one case, a pediatric renal transplant patient with severe oseltamivir-resistant influenza A H1N1 recovered following peramivir therapy; however, this patient also had “aggressive critical care support” and reduction in his immunosuppression [7]. In 1 HSCT patient, peramivir was associated with recovery from severe pandemic influenza A H1N1, but peramivir use was concurrent with lymphocyte recovery and oseltamivir use and was preceded by triple combination antiviral therapy with oseltamivir, oral ribavirin, and oral amantadine, as well as inhaled ribavirin and intravenous immunoglobulin [8]. There were no detected oseltamivir H275Y resistance mutations. Additionally, the role of peramivir in the management of patients with documented resistance to oseltamivir has been called into question. In 1 allogeneic HSCT patient with oseltamivir-resistant virus due to neuraminidase mutation H275Y, virus replication continued despite peramivir therapy [9]. Overall, the limited data do not allow conclusions about the efficacy of peramivir in immunocompromised populations [10].

#### Zanamivir

Inhaled zanamivir is another NAI approved for influenza therapy. There are limited data on inhaled zanamivir in transplant populations, but the tolerability and outcomes suggest that it is a reasonable option, although further studies are needed [10]. Investigational IV zanamivir has been available on a compassionate-use basis in the setting of failure of other antivirals, with contraindication to inhaled zanamivir, or as part of a clinical trial. Failure to absorb oseltamivir and the development of oseltamivir-resistant (specifically, H275Y) mutations were reported as indications for usage [10–12]. In a retrospective study of IV zanamivir in critically ill patients with pandemic influenza A H1N1 who had already received at least 3 days of oseltamivir prior to IV zanamivir, 8 of 13 (62 %) were immunocompromised [11]. Seven of the patients developed acute respiratory distress syndrome, and 5 patients (63 %) died. Several case reports of pediatric immunocompromised hosts, including those with HSCT, leukemia, and liver transplantation, appear in the literature, predominantly with oseltamivir-resistant pandemic influenza H1N1 viral isolates. While survival results are mixed for these patients, most report a decrease in the viral load as evaluated by polymerase-chain reaction (PCR) threshold cycle values. Most of the remaining case reports relate to pediatric transplant patients, who had mixed survival results [13–16]. Data on IV zanamivir in the immunocompromised population remain scant, but there may be benefit for its use in oseltamivir-resistant influenza infections.

#### Laninamivir Octanoate

Laninamivir octanoate (CS-8958) is a long-acting, inhaled NAI that was approved in Japan in October 2010. Given its persistence in the airway, a single dose has generally been used in most studies to date. Laninamivir octanoate has shown efficacy in seasonal influenza, oseltamivir-resistant influenza A (H1N1), and influenza H5N1 viruses in immunocompetent subjects [2]. In a postmarketing study of laninamivir octanoate in 3,524 patients, only 8 (0.2 %) were classified as having “diseases accompanied by a reduction in immune function” [17]. Of that group, 7 (86 %) were categorized as responding to treatment, with fever resolution and relief from influenza symptoms. At present, there is little data on the efficacy of laninamivir octanoate in immunocompromised persons.

#### DAS181

The sialidase fusion protein DAS181 is another novel agent that has activity against both influenza and parainfluenza viruses [18, 19]. The mechanism of action of DAS181 is to cleave the terminal sialic acid linkages on the host cells to reduce binding and infectivity of the virus [18, 20]. In vitro and in vivo studies suggest that DAS181 is active against oseltamivir-resistant strains of influenza. Currently, it has been studied in animal models and one phase II trial [20, 21, 22–24]. In the phase II study, the patients were infected with seasonal influenza A H3N2, pandemic influenza A 2009 H1N1, or influenza B [20]. DAS181 was associated with a statistically significant reduction in viral load from days 1–3 in these otherwise generally healthy patients. One death occurred in a female patient with previously undiagnosed HIV infection, who expired from respiratory failure, with severe pneumonia and *H. influenzae* and *S. aureus* isolated from sputum cultures. Overall, further evaluation of DAS181 and influenza infection is necessary, particularly in immunocompromised populations (see below for data on the management of parainfluenza virus).

#### Respiratory Syncytial Virus

Respiratory syncytial virus (RSV), an enveloped nonsegmented RNA virus in the paramyxovirus family, causes URIs and LRTIs in immunocompromised hosts. RSV infection has been linked to significant morbidity and mortality in this population. Progression to LRTI is associated with increased mortality after HSCT, while RSV has been epidemiologically associated with the development of bronchiolitis obliterans syndrome (BOS) in adult lung transplant recipients. Various therapies have been assessed for an impact on disease progression, morbidity, and mortality, and several emerging therapeutics are under investigation.

## Ribavirin

Ribavirin is a guanosine analog active against RNA and DNA viruses that is available for oral, intravenous, or aerosolized administration. It was discovered more than 40 years ago, and the majority of research and clinical use centers on inhaled and aerosolized forms of the drug; there is emerging data on the use of oral ribavirin for the management of RSV. Ribavirin orally is ~45 %–65 % absorbed without food. The half-life is ~12 days when administered over time, and there is extensive accumulation in all tissues [25]. It has activity against influenza, measles, West Nile virus, RSV, and other viruses. When oral ribavirin became available, Pelaez described its use in conjunction with steroids in 5 adult lung transplant recipients, finding oral therapy less costly than aerosolization; this intervention was not directly compared with placebo or other formulations of ribavirin [26]. Additionally, a comparison between outcomes for lung transplant recipients receiving oral ( $n=6$ ) and inhaled ( $n=15$ ) ribavirin in conjunction with steroids and IVIG was performed at a single center. There were no significant differences reported for survival or BOS development/progression at 6 months postinfection in this cohort [27]. Studies assessing the concentration of oral ribavirin in lung fluid in transplant patients have not been conducted. Despite limited data on its efficacy in clearing RSV infection in solid organ transplant (SOT), ribavirin, especially in the aerosolized form, has additionally been evaluated in conjunction with other therapies, including steroids, IVIG, and palivizumab (see below), and remains a standard part of many local treatment protocols.

## Palivizumab/Motavizumab/MEDI-557

Palivizumab, motavizumab, and MEDI-557 are all antibodies against RSV fusion protein. Currently, only palivizumab is approved for prophylaxis of RSV infection in a select group of premature infants and children <2 years of age with uncorrected cyanotic congenital heart disease or chronic lung disease. Motavizumab is 10 times more potent than palivizumab. In a randomized study, motavizumab exhibited increased skin reaction adverse events but similar clinical outcomes as palivizumab [28]. MEDI-557 has a longer half-life, which may allow for less frequent dosing. Neither motavizumab nor MEDI-557 has been studied in immunocompromised hosts to date.

Palivizumab has been assessed in both HSCT and lung transplant recipients. The largest study of palivizumab evaluated two groups of HSCT recipients [29••]. In the first group, 6 HSCT patients without RSV received palivizumab, noting a serum half-life of 22.4 days. An additional 15 HSCT patients with RSV (URTI=3, LRTI=12) received palivizumab in addition to aerosolized ribavirin. Palivizumab was cleared more rapidly in the RSV-infected group with a half-life of 10.7 days.

All patients with URTI recovered without progression to LRTI, while 10 patients with LRTI survived past the 28-day study period. In addition, palivizumab given to 16 HSCT patients along with infection prevention measures, including patient cohorting, visitor screening, and hand hygiene, was successful when administered prophylactically during a nosocomial outbreak of RSV [30]. Finally, palivizumab was used as part of a multidrug regimen that included inhaled ribavirin, steroid, and IVIG in 23 lung transplant recipients with RSV [31]. Forced expiratory volumes in one second (FEV1) after treatment were similar to baseline. However, progression of BOS was not impacted by RSV therapy; patients with higher-grade BOS at infection had more rapid declines in FEV1 over the follow-up period compared to those without BOS at infection.

## ALN-RSV01

ALN-RSV01 is a small interfering RNA that can enter the cell to target RSV-specific viral mRNA and interferes with viral replication. Two randomized placebo-controlled trials of this aerosolized agent have been performed in lung transplant recipients, while no studies have been performed in HSCT to date. Zamora and colleagues reported on 24 lung transplant recipients with confirmed RSV who received ALN-RSV01 ( $n=16$ ) or placebo ( $n=8$ ) for 3 days [32•]. Both cumulative total of the daily symptom score ( $p=.035$ ) and new or progressive BOS rates at day 90 ( $p=.027$ ) were lower in the ALN-RSV01 recipients. Simon and colleagues studied an additional 87 lung transplant recipients with RSV who received 5 days of ALN-RSV01 or placebo [33•]. With a longer follow-up period of 180 days, the ALN-RSV01-treated patients had lower rates of new or progressive BOS, as compared with placebo (13.6 % vs. 30.3 %,  $p=.058$ ). The treatment effect was seen regardless of ribavirin coadministration.

## Novel RSV-Specific Antivirals

RSV604 (previously A-60444) is reported to have novel anti-RSV activity against both subtypes A and B. After a phase I safety and tolerability study in healthy controls, studies were planned in HSCT recipients with RSV [clinicaltrials.gov (NCT00232635)], but further information and results are not yet available in the literature.

Two fusion inhibitors that act by blocking an RSV fusion protein are under investigation. TMC 353121 has been evaluated in mouse and monkey models showing in vivo anti-RSV activity. MDT-637, which is given via a dry powder aerosol, was successfully tested in 2011–2012 in phase I studies for safety and tolerability in healthy and asthmatic adults. Neither agent has been evaluated for use in immunocompromised hosts to date.

ALX-0171 nanobodies also bind to RSV fusion protein F, allowing for the attachment of the virus to the cell, but not fusion with the cell precluding infection [34]. A novel antibody that arose from a discovery in dromedaries, ALX-0171 can be delivered directly to the lung via aerosolization. ALX-0171 has been studied in healthy male volunteers in a phase I randomized placebo-controlled protocol to evaluate dosing, safety, tolerability, and pharmacokinetics of the agent but has not been tested in immunocompromised hosts.

### Parainfluenza Virus

Parainfluenza virus (PIV), a single-stranded, enveloped RNA virus, has been described as causing severe infections, leading to increased morbidity and mortality in immunocompromised populations. Previously published reports described infection in up to 7 % of stem cell transplants and up to 16 % of lung transplant patients [35].

#### DAS181

There have been several published case reports describing treatment of PIV type 3 (PIV3) LRTI in the immunocompromised population with DAS181, whose mechanism has been described [36•, 37•, 38•]. Two patients with unilateral lung transplants with severe lower respiratory tract PIV3 disease received 5 days of therapy with DAS181. Symptoms improved in both patients soon after treatment started. Reduction of viral load occurred in both cases, and both patients were discharged after recovery from the illness. Side effects included mild elevations in alkaline phosphatase, which resolved after completion of therapy. In HSCT, two cases have been described [37•, 38•]. An autologous HSCT recipient with a history of multiple myeloma and an allogeneic HSCT recipient recovered after 5 and 3 days of therapy with DAS181, respectively. They also had variable reductions in their viral load during and after therapy. However, 1 patient experienced relapse of both PIV3 infection and primary disease, at which point further therapy for PIV3 was not pursued [37•].

### Rhinovirus

The human rhinovirus (HRhV), a member of the Picornavirus genera, has >100 serotypes in three different species: A, B, and the more recently characterized C [39]. The spectrum of disease in immunocompromised populations also ranges from mild to severe [40–42]. Treatment for HRhVs remains supportive, since no active agents are currently commercially available [43]. A new oral drug vapendavir or BTA793 (Biota Pharmaceuticals, Inc., Melbourne, Australia), which binds to the viral capsid to inhibit/interfere with receptor binding and

subsequently prevent further infection, is under development. A phase 2 randomized, double-blind, placebo-controlled study in asthmatics with HRhV infection showed greater mean reduction in asthma score and higher evening peak expiratory flow in the vapendavir group, versus placebo [44]. Additional investigation in immunocompromised hosts is needed.

### Adenovirus

Adenovirus (AdV) is a double-stranded, nonenveloped DNA virus. There have been more than 60 serotypes and seven species (A–G) identified [45, 46]. AdVs cause both disseminated and localized disease, such as pneumonia in both immunocompetent and immunosuppressed populations [45, 47–49]. Nucleoside analogs ribavirin, ganciclovir, and cidofovir have shown in vitro activity to AdV; however, only cidofovir has been recommended as treatment for AdV infection [50]. Most recently, a lipid-conjugate, oral form of cidofovir, CMX001 (Chimerix, Durham, NC), has been studied in both HSCT and SOT. First, under an eIND program to treat severe AdV infections [51••], 57 children and adults were enrolled, 83 % (47) with HSCT and 12 % (7) after SOT. While 53 % survived to study completion, 9 deaths (6 with disseminated infection and 3 with localized infection) were attributed to AdV disease, while 13 others expired due to other causes. The survival of those with localized lung disease was not reported. Florescu reported on 17 patients who received CMX001 as salvage therapy for disseminated AdV, 13 of which were available for analysis (11 HSCT, 1 SOT, 1 severe combined immunodeficiency CID) [52••]. Respiratory disease was diagnosed in 3 patients, of which 1 patient expired secondary to AdV pneumonia. Nine patients experienced a >99 % decrease in plasma viral load by the end of treatment or follow-up period. In patients who responded to CMX001 therapy with decreased viral load, survival was improved from median 196 days versus 54.5 days ( $p=.4$ ), as compared with nonresponders. CMX001 has been well-tolerated and should be explored further as a therapeutic option for AdV infections in immunocompromised populations.

### Coronavirus

The enveloped RNA virus human coronavirus (HCoV) of the family *Coronaviridae* generally causes infections during the winter respiratory viral season. Usually mild in immunocompetent hosts, HCoV infection in immunosuppressed populations can lead to significant lower respiratory tract disease [43, 53]. Furthermore, emerging HCoVs such as severe acute respiratory syndrome-associated HCoV (SARS-CoV) in 2002–2003 and the more recently identified novel coronavirus (nCoV, now MERS) in 2012–2013 have prompted further



concern for developing therapeutics against this family of viruses. While effective antiviral agents are currently lacking [43], discovery and in vitro evaluation of novel HCoV therapeutics is underway, with investigation of entry inhibitors, human monoclonal antibodies, proteasome inhibitors, and even a scorpion venom peptide [54–57]. For now, HCoV treatment remains supportive.

## Conclusions

The current antiviral armamentarium against respiratory viral infections aside from influenza therapies is limited, resulting in few options to impact the associated morbidity and mortality from these illnesses in immunocompromised hosts. New drugs are currently in development that could have a significant impact on treating these infections. Some of the drugs, such as laninamivir octanoate, are available in certain markets, while others can be accessed through the eIND mechanism in the United States. Still other antivirals are in early clinical and preclinical investigation stage. Additional investigation is needed, particularly in immunocompromised hosts, to expand the options for effective therapy for respiratory viral infections.

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## Compliance with Ethics Guidelines

**Conflict of Interest** Dana Hawkinson, Daniel Hinthorn, and Lara Danziger-Isakov declare that they have no conflict of interest

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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