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The enteroviruses: Problems in need of treatments

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Summary Specific antiviral therapy is currently not available for enterovirus (EV) infections. Poliomyelitis, EV 71 neurologic disease, and neonatal EV disease are three manifestations of EV infections that exemplify the importance of developing antivirals for EV infections. Despite tremendous strides in the effort to eradicate polio through vaccination, challenges remain, including the potential for transmission of neurovirulent vaccine-derived polioviruses which have genetically reverted from live-attenuated, oral poliovirus vaccine virus. EV 71 emerged in the late 1990s in eastern Asia as a neurovirulent virus that causes large outbreaks of hand-foot-mouth disease, herpangina, and fever, and, in some children, meningitis, acute flaccid paralysis, and brainstem encephalitis complicated by pulmonary edema and cardiopulmonary collapse. EV infections in neonates can cause severe disease characterized by meningoencephalitis, myocarditis, pneumonitis, and/or hepatitis and coagulopathy. Prototypic agents for specific therapy of EV infections that act upon numerous potential viral targets exist. Three candidate compounds are currently in development: pleconaril (active against many EVs), V-073 (anti-poliovirus), and BTA-798 (active against many rhinoviruses and EVs). The three conditions described illustrate why development of antiviral medications for EV infections is a medically important need.

Introduction

The enteroviruses (EVs), a genus in the Picornaviridae family (which also includes the rhinoviruses, hepatitis A virus, and parechoviruses), include more than 90 distinct viral serotypes. Historically, these viruses were subcategorized as polioviruses (PVs), coxsackieviruses A and B, echoviruses, and, more recently, newer, numbered EVs. Although current classification is based on genotypic categories, these historical groupings are still commonly used when describing associations with clinical manifestations.

EV infections are associated with a wide variety of clinical manifestations, including non-specific febrile illness; exanthems; respiratory illness; herpangina; hand-

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foot-mouth disease; hemorrhagic conjunctivitis; myocarditis and pericarditis; neurologic disease, including meningitis, encephalitis, and acute flaccid paralysis; chronic and/or disseminated infection in immunocompromised patients, including agammaglobulinemic patients and transplant recipients; and perinatal infections. Many entities have historically been associated with specific EV groups or specific serotypes, e.g., exanthems and echovirus 9, herpangina and coxsackie A viruses, hand-foot-mouth disease and coxsackievirus A16, hemorrhagic conjunctivitis and EV 70 and coxsackievirus 24, myocarditis and coxsackie B viruses, and acute flaccid paralysis and PVs. However, new or increasingly important associations manifest over time. For example, EV 68 has recently emerged as an important cause of severe respiratory disease worldwide, and coxsackievirus A6 has recently been reported in several areas of the world as a cause of unusually severe hand-foot-mouth disease and more extensive rash illness in children and adults.[1,2] EV 71 has been a cause of widespread and severe epidemics of hand-foot-mouth disease, herpangina, encephalitis, and acute flaccid paralysis since the late 1990s.

At the current time, specific antiviral therapy is not available for EV infections, although efforts to develop such treatment continue. This review discusses three EV entities which serve as examples of why development of EV treatment is important and summarizes the current status of EV drug development.

Poliovirus and poliovirus eradication

The polio eradication initiative

The Global Polio Eradication Initiative was launched in 1988 by the World Health Assembly, with oral poliovirus vaccine (OPV) to be the used as the primary tool in the eradication effort. In that year, 350,000 cases of polio were reported and the disease was endemic in 125 countries. Progress since 1988 has been remarkable. In 1999, one of the three strains of PV, wild type PV 2 was eradicated. In 2010, 1352 cases of polio were reported, with a further reduction to 650 cases in 2011. Despite these great successes, the goal of eradication has proved challenging over the past decade. Challenges included a small number of countries with ongoing endemic disease (Afghanistan, Pakistan, India, and Nigeria) and periodic importation from these countries into countries that had previously become polio-free but had maintained relatively low levels of vaccination coverage more recently, particularly on the African continent. Importations led to re-established transmission in some countries, e.g., Chad, Democratic Republic of the Congo, Angola, and Sudan, and secondary spread to other countries. An additional challenge has been outbreaks of OPV-derived PV2 viruses that had acquired the capacity to be neurovirulent and circulate within a population through genetic reversion, so-called circulating vaccine-derived polioviruses (cVDPVs). Currently, three countries, Afghanistan, Pakistan, and Nigeria, continue to have endemic disease. A significant achievement was the declaration in January 2012 that India was no longer polio-endemic, having had no wild-type disease in the preceding year.[3–6]

Challenges with oral poliovirus vaccine

Although widespread use of OPV has been associated with great successes, its use may have several negative consequences that can hinder the ultimate eradication of polio. These include rare cases of vaccine-associated paralytic poliomyelitis (VAPP) due to genetic reversion to neurovirulence of vaccine virus in vaccine recipients or their close contacts, cVDPVs which not only are neurovirulent but have the capacity to circulate, and immune-deficiency-related vaccine-derived polioviruses (iVDPVs). Immune deficient hosts, particularly those with antibody deficiencies, may be unable to eliminate OPV vaccine strains and can shed iVDPVs for many years and serve as an ongoing reservoir for vaccine-derived virus introduction in a community. Additionally, OPV-derived virus in these individuals can revert to neurovirulence many years after initial exposure, as exemplified in a recently described case.[7–10]

Poliovirus antiviral initiative

In response to persisting challenges to achieving the goal of polio eradication, the National Research Council Panel of the U.S. National Academies was commissioned in 2005 by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) to consider the potential role for antiviral drugs in the polio eradication effort. The conclusion of this panel was that at least two agents working by different mechanisms, so as to minimize the emergence of resistance, should be developed to assist in the eradication effort. In 2007, the WHO and CDC endorsed this recommendation and established the PV antiviral effort.

Why would antivirals be useful in the polio eradication effort? It is anticipated that after early evidence of eradication, programmatic decisions may favor curtailing widespread use of OPV due to the threat of VAPP, cVDPVs, and iVDPVs from ongoing vaccination. Cost and logistical considerations may prove to be barriers to more widespread use of inactivated poliovirus vaccine (IPV) in place of OPV. If high levels of vaccine-induced immunity are not maintained, susceptible populations may be at risk of infection if exposure to PV, either in the form of OPV-derived virus (either cVDPs or iVDPs being shed for prolonged periods) or, possibly, laboratory release of PV, occurs. If this scenario were to develop, broad re-introduction of OPV may not be desirable as it may perpetuate the problem by creating more cVDPs and iVDPs, and IPV, which does not induce mucosal and herd immunity, may be too inefficient to abort outbreaks. Antivirals active against PVs, on the other hand, may be useful tools to treat acute polio infections, eradicate persistent infection in vaccine-derived poliovirus shedders, and contain outbreaks, both by treatment of infected individuals and prophylaxis of exposed contacts, with or without adjunctive vaccination.[7–9]