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Review

Highly pathogenic RNA viral infections: Challenges for antiviral research

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Abstract

A number of RNA viruses can cause severe disease when transmitted to humans from an animal reservoir. One of them, the recently emerged H5N1 subtype of influenza A virus, has caused several hundred cases of severe disease when transferred directly from domestic poultry. This or another avian subtype could potentially evolve to a form more transmissible by the respiratory route or reassort with a circulating strain to initiate a pandemic. Other zoonotic RNA viruses cause sporadic single cases or outbreaks of hemorrhagic fever or encephalitis that spread inefficiently from person-to-person, and thus remain confined to the geographic range of the maintenance host. RNA viral infections of farm animals, such as foot and mouth disease and classical swine fever, also pose a major threat to human well-being through economic loss and impaired nutrition. Only a few licensed antiviral drugs are available to prevent or treat these conditions. Medications that inhibit the replication of influenza virus might be used in an epidemic both to treat severe disease and to block the spread of infection. The guanosine analog ribavirin has been used to treat a few types of hemorrhagic fever, but there is no specific therapy for the others, or for any type of RNA viral encephalitis. The quest for new antivirals is being supported by government programs and new collaborative research networks. Major efforts will be required to identify active compounds, test their efficacy in laboratory animals, obtain approval for human use and develop rapid diagnostic methods that can identify patients early enough in the disease course for treatment to be of benefit.

Keywords: Viral hemorrhagic fever; Viral encephalitis; Arbovirus; Influenza; H5N1 influenza; Filovirus; Flavivirus; Yellow fever; Lassa fever; Lassa virus; Ebola hemorrhagic fever; Marburg hemorrhagic fever; Junin virus; Argentine hemorrhagic fever; Hantavirus; Hantavirus pulmonary syndrome; Crimean-Congo hemorrhagic fever; Arenavirus; Bunyavirus; Alphavirus; Japanese encephalitis; Zoonosis; Antiviral therapy; Antiviral drug; Emerging infectious diseases; Livestock diseases; Foot-and-mouth disease; Biodefense

Contents

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1. Introduction

This special issue of *Antiviral Research* reviews current approaches to the treatment of highly pathogenic RNA viral infections and efforts to develop new therapies. In contrast to less virulent agents such as the rhinoviruses, which persist through continuous person-to-person transmission, the RNA viruses discussed in this issue are maintained in animals, and can cause severe illness with high case fatality rates or significant residual disability when transferred to humans. This introductory article reviews the problem of RNA viral zoonoses and briefly examines each of the diseases covered in this issue. Two additional introductory papers discuss licensed and experimental therapies: that by Leyssen et al. focuses on nucleoside analogs and other "small molecules," while that by Spurgers et al. reviews sequence-based therapies using antisense molecules and siRNA (Leyssen et al., 2008; Spurgers et al., 2008).

Diseases caused by nine RNA viruses from six different families have been chosen as the subjects of articles in this special issue (Table 1). They can be divided into three groups. The first consists of illness caused by influenza virus. Various viral subtypes produce sporadic cases of conjunctivitis or respiratory disease in humans when transferred directly from infected birds, but also have the proven capacity to evolve into highly transmissible agents that spread by the airborne route to cause global epidemics. Current concern focuses on the H5N1 virus, which was first recognized as a highly virulent pathogen of domestic poultry and humans in Hong Kong in 1997 and re-emerged in Southeast Asia in 2003. The second group consists of more than 30 different types of severe hemorrhagic fever or encephalitis caused by zoonotic RNA viruses. In contrast to influenza virus, the causative agents discussed in this review have so far proven incapable of sustained human-to-human transmission, causing only single cases or small outbreaks of illness within the regions occupied by their maintenance hosts or arthropod vectors. However, they still impose a significant burden on public health resources, through a frequent requirement for prolonged hospitalization, high case fatality rates and the danger some of them pose to health care workers. Many have the potential to be used as bioterror weapons. The third group of pathogens consists of RNA viruses that infect farm animals, causing major financial losses and impairing the nutrition of people dependent on them for food. As in the case of some hemorrhagic fever and encephalitis viruses, certain livestock pathogens could also be used in terrorist attacks against the agricultural industry.

2. Potential for new drug development

Specific therapies exist for only a few of the diseases discussed in this issue. The most effort has gone into developing drugs for influenza, probably because the prospect of treating millions of people in a global epidemic has encouraged pharmaceutical companies to undertake the necessary research and development efforts. RNA viral encephalitis and hemorrhagic fever have received much less attention, in part because the diseases occur predominantly in underdeveloped countries that lack the infrastructure for clinical trials and the resources to pay for expensive medications. Only a single licensed drug, ribavirin, is in use against any of these infections; its efficacy against a few types of viral hemorrhagic fever has been reported only in observational studies.

Surprisingly, even though RNA viral infections of livestock have cost the industrialized countries many billions of dollars in lost trade over the past decade, little effort has been made to develop antivirals against these diseases, and none are in veterinary use. As discussed by Goris et al. (2008), the focused use of antiviral therapy could be a useful control measure in outbreaks of foot-and-mouth disease and other conditions, supplementing or replacing such costly and inefficient strategies as emergency vaccination and mass slaughter.

Fortunately, the absence of approved therapies does not mean that no compounds inhibit highly pathogenic RNA viruses. As reviewed in this issue, a considerable number of substances show good activity *in vitro*, and some have been protective in the large number of laboratory animal models that are now being used to assess drug efficacy (Gowen and Holbrook, 2008; Holbrook and Gowen, 2008; Leyssen et al., 2008; Spurgers et al., 2008). The number of candidate medications will increase as new technology and sources of financial support become available. As described here, a variety of US government resources have been made available to aid in this effort, and new multinational research networks are providing a wealth of data on viral structural proteins, replication mechanisms and potential drug targets (Coutard et al., 2008; Greenstone et al., 2008; Kuhn and Canard, 2008). Procedural innovations such as the US Food and Drug Administration's recently promulgated "Animal Rule" are also helping to smooth the path for drug development (Roberts et al., 2008).

3. Developing new therapies—and finding the patients

Because RNA viral zoonoses cannot be eradicated, countermeasures will always be needed to prevent and treat them. Some diseases will increase in incidence over coming decades,