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Review Article

Tick-borne viruses: A review from the perspective of therapeutic approaches

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ABSTRACT

Several important human diseases worldwide are caused by tick-borne viruses. These diseases have become important public health concerns in recent years. The tick-borne viruses that cause diseases in humans mainly belong to 3 families: Bunyaviridae, Flaviviridae, and Reoviridae. In this review, we focus on therapeutic approaches for several of the more important tick-borne viruses from these 3 families. These viruses are Crimean-Congo hemorrhagic fever virus (CCHF) and the newly discovered tick-borne phleboviruses, known as thrombocytopenia syndromevirus (SFTSV), Heartland virus and Bhanja virus from the family Bunyaviridae, tick-borne encephalitis virus (TBEV), Powassan virus (POWV), Louping-ill virus (LIV), Omsk hemorrhagic fever virus (OHFV), Kyasanur Forest disease virus (KFDV), and Alkhurma hemorrhagic fever virus (AHFV) from the Flaviviridae family. To date, there is no effective antiviral drug available against most of these tick-borne viruses. Although there is common usage of antiviral drugs such as ribavirin for CCHF treatment in some countries, there are concerns that ribavirin may not be as effective as once thought against CCHF. Herein, we discuss also the availability of vaccines for the control of these viral infections. The lack of treatment and prevention approaches for these viruses is highlighted, and we hope that this review may increase public health awareness with regard to the threat posed by this group of viruses.

Contents

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Introduction

Tick-borne viruses are a group of viruses with significant worldwide importance in public health and as such a global concern. Currently, there is no effective therapeutic agent or vaccine for most of these viruses. Novel viral mutants and different variants can emerge and may potentially become a public health threat. These new emerging viruses could also pose a biosecurity threat. The aim of this review is to increase the public awareness of this group of viruses, particularly with regard to the possible treatment approaches and antiviral drugs for the management, control, and prevention of the diseases caused by these viruses. Generally, the therapeutic strategies comprise of (i) vaccination; (ii) administration of high-titer antibodies; and (iii) treatment with antiviral drugs. In this review, we have focused on tick-borne viruses that are of public health importance and the antiviral drug perspective for the treatment of the diseases caused by them.

Family Bunyaviridae

Crimean-Congo hemorrhagic fever virus

Crimean-Congo hemorrhagic fever virus (CCHFV; genus: Nairovirus; family: Bunyaviridae) was first identified in 1944 in the Crimean Peninsula (Chumakov et al., 1963; Mourya et al., 2012), and it was then isolated from a patient in Kisangani, Congo, in 1956 (Simpson et al., 1967; Mourya et al., 2012). This virus, which is maintained in nature by ixodid species (Labuda and Nuttall, 2004) and is transmitted by *Hyalomma* ticks (Tekin et al., 2010), has been associated in a series of outbreaks with a large geographical distribution across Europe, Middle East, Asia, and Africa (Hoogstraal, 1979; Whitehouse, 2004; Flick and Whitehouse, 2005; Papa et al., 2010; Tekin et al., 2010; Ergonul, 2012). Besides transmission of the virus by ixodid ticks, CCHFV can be transmitted by contact with tissues and excreta or secreta of infected animals or humans (Keshtkar-Jahromi et al., 2011; Ergonul, 2008; Whitehouse, 2004). Early signs of the disease typically include fever, hypotension, conjunctivitis, and cutaneous flushing or skin rash. Later, patients may have signs of progressive hemorrhagic diathesis, similar to petechiae, and mucous membrane and conjunctival hemorrhage hematuria, hematemesis, and melena. Disseminated intravascular coagulation (DIC) and circulatory shock may ensue (Ergonul, 2012). The mortality rate of CCHF is between 9% and 50% (Ergonul, 2008).

Issues concerning the treatment and prevention of CCHF

There is currently no effective vaccine available for CCHF, although several vaccine candidates have been developed and evaluated. One example of a candidate vaccine for CCHF is the inactivated mouse brain vaccine, which was used on a small scale in the former Soviet Union and Bulgaria on several hundred human volunteers (Tkachenko et al., 1971; Vasilenko, 1973). Despite the vaccine being able to induce high detectable antibody levels, no sufficient clinical trials were performed as there were concerns about using mouse-brain vaccines, which have the potential to cause autoimmune responses. Additionally, there is a lack of commercial value for the vaccine as CCHF is a disease confined to poor-resource countries.

More recently, a DNA vaccine containing the CCHF genome M segment was developed, and it was demonstrated that it induces neutralizing antibodies in mice, as well as antibodies that immunoprecipitate with the M segment expression products (Spik et al., 2006; Keshtkar-Jahromi et al., 2011). However, the protective effect of the vaccine was not evaluated. Currently, management of CCHF is based on general supportive measures and monitoring of the patient's hematologic and coagulation status, with replacement of cells and factors as needed (Ergonul, 2008).

To date the only drug that is placed on the WHO essential medicines list to be used against CCHFV infection is ribavirin (Ergonul, 2006); however, there are many contradictions with regard to the efficacy of this drug for CCHF disease. Ribavirin inhibits the growth of CCHFV in vitro and in experimentally infected mice (Watts et al., 1989; Tignor and Hanham, 1993). There is evidence about the effectiveness of this drug in patients following oral and intravenous administration (Mardani et al., 2003; Elaldi et al., 2009). However, in one randomized controlled trial published on this topic, there was no significant positive effect in the clinical or laboratory parameters after administration of ribavirin in CCHF patients (Koksal et al., 2010). In a meta-analysis of 21 unique studies including one randomized controlled trial of ribavirin to investigate the effect of ribavirin in CCHF patients, it was noted that the current data available are insufficient to understand the efficacy of the drug (Soares-Weiser et al., 2010). For example, studies in which ribavirin was combined with cycloferon, which is an interferon inducer, either in the form of solution or tablets, shortened the period of the fever in CCHF patients, minimized the intoxication syndrome, promoted earlier resolution of hemorrhagic eruption, and lowered the frequency of complications, which improved the disease prognosis (Cherenov et al., 2012; Romantsov et al., 2012). Administration of corticosteroids together with ribavirin was also reported to be useful, particularly during early stages of the disease–however, this experience was limited to an observational study of only 6 patients (Jabbari et al., 2006).

Currently, ribavirin is used in most endemic countries and ethical issues about using a randomized trial have been raised (Arda et al., 2012). Researchers should therefore consider how ribavirin therapy might be further evaluated without violating ethical guidelines. Given the high fatality rate associated with CCHF, well-designed multi-center and random-controlled trials are urgently needed to provide evidence-based data about the efficacy of ribavirin (Maltezou and Papa, 2011). Besides ribavirin, there are some other studies to find effective antiviral compounds against CCHFV, including the in vitro inhibitory properties of exogenous nitric oxide (NO) on CCHFV replication (Simon et al., 2006). Type-I interferon (IFN) has significant antiviral activity against many hemorrhagic fever viruses in vitro, and in animal models, Karlberg et al. (2010) in an in vitro study showed significant antiviral activity of a natural IFN-α produced in human leukocytes (multiferon) compared to 2 recombinant IFN-α preparations (roferon A and intron A) against CCHFV. However, there are data suggesting that CCHFV possesses mechanisms to defeat the IFN-induced defense mechanisms by delaying IFN secretion for 48 h post infection (Andersson et al., 2008). In one study using a small interfering RNAs (siRNAs) approach, it was shown that the IFN-induced MxA GTPase is a major factor mediating the antiviral effect against CCHFV, and the IFN-α inhibits the growth of CCHFV in