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Treatment of Crimean-Congo hemorrhagic fever

Onder Ergonul

Marmara University, School of Medicine, Infectious Diseases and Clinical Microbiology Department, Istanbul, Turkey

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Abstract

Crimean-Congo hemorrhagic fever (CCHF) has the most extensive geographic range of the medically significant tick-borne viruses, occurring from western China across southern Asia to eastern Europe and South Africa. The causative agent is a negative-sense, single-stranded RNA virus in the genus *Nairovirus*, family Bunyaviridae. In published reports, the case fatality rate has generally ranged from 10% to 50%. Sporadic cases and outbreaks of the disease have increased during the past decade across the endemic region. CCHF was first diagnosed in Turkey in 2002, but since then more than 1100 cases have been confirmed by IgM serology or RT-PCR, with a fatality rate of just over 5%. Simple methods are available for the *in vitro* evaluation of antiviral drugs, but because CCHF virus does not cause disease in its reservoir species or in laboratory animals other than suckling mice, methods are lacking for *in vivo* efficacy testing. Intravenous or oral ribavirin has been used in several countries to treat the disease for more than 20 years. Evidence of its efficacy is limited to observational studies, and placebo-controlled trials may be impossible to perform for ethical reasons. However, careful analysis of properly stratified observational studies can be used to assess the effects of treatment. This article reviews current approaches to the treatment of CCHF, focusing on the use of ribavirin and hematological support, and discusses prospects for future research.

Keywords: Crimean-Congo hemorrhagic fever; Ribavirin; Bunyavirus; Emerging infections; Viral hemorrhagic fever; Arbovirus; Antiviral therapy; Biodefense

1. Introduction

Crimean-Congo hemorrhagic fever (CCHF) has the most extensive geographic range of the medically significant tick-borne viruses, occurring in parts of Africa, Asia, eastern Europe, and the Middle East (Hoogstraal, 1979; Watts et al., 1989; Whitehouse, 2004; Ergonul, 2006; Ergonul and Whitehouse, 2007). CCHF virus (CCHFV) belongs to the genus *Nairovirus* in the family Bunyaviridae. Humans become infected through the bites of ticks, by contact with a patient during the acute phase of infection, or through exposure to the blood or tissues of viremic livestock (Whitehouse, 2004). In published reports, the case fatality rate has generally ranged from 10% to 50%. The admission of unrecognized CCHF cases to hospitals poses a particular threat to medical workers in endemic areas (Fisher-Hoch et al., 1995; Van Eeden et al., 1985).

The incidence of sporadic cases and outbreaks of CCHF has increased across the endemic region during the past decade (Formenty et al., 2007). The first case in Turkey was diagnosed in 2002, but by the end of 2006 more than 1100 patients with a confirmed diagnosis by IgM serology or PCR had been identified, with a fatality rate of 5.4% (Ministry of Health, 2007; Vatansever et al., 2007). The apparent increase in incidence may reflect both greater human exposure to infected ticks and more widespread recognition of the disease by health care workers (Vatansever et al., 2007). It is not known whether viruses from different regions differ in their virulence for humans. The widespread geographical distribution of CCHFV, its ability to produce severe human disease and concerns about its potential use as an agent of bioterrorism combine to make the virus an important human pathogen (CDCP, 2005).

As discussed in detail below, a number of observational studies have indicated that treatment with the antiviral drug ribavirin is beneficial for CCHF, but no placebo-controlled trials have been performed. Simple methods of *in vitro* drug testing are available, but efforts to develop improved therapies have been hindered by the lack of animal models other than infection of suckling mice (Nalca and Whitehouse, 2007; Paragas et al., 2004). This article reviews current approaches to treatment, focusing principally on the use of ribavirin and hematological support, and discusses how evidence of therapeutic benefit can be assessed even when prospective placebo-controlled studies cannot be performed. Other potential therapies, such as interfer-

E-mail address: onderergonul@yahoo.com.

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ons and immunotherapeutical options, including measures currently in use for the treatment of septic shock, are also examined.

2. Clinical features and pathogenesis

CCHF shares many clinical features with other types of viral hemorrhagic fever. After an incubation period of less than a week, patients become abruptly ill with fever, severe headache and muscle aches, nausea, diarrhea and other nonspecific symptoms. Severe cases progress rapidly to disseminated intravascular coagulation (DIC), bleeding and shock (Ergonul, 2007a). Various forms of hemorrhage, including petechiae, large ecchymoses, melena and hematemesis tend to be more prominent in CCHF than in other types of viral hemorrhagic fever. As in other types of viral hemorrhagic fever, proinflammatory cytokines, including interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha, are present in the plasma of patients; levels are significantly higher in fatal than in nonfatal cases (Ergonul et al., 2006a).

Circulating virus in the bloodstream can be detected soon after the onset of illness, together with a drop in the platelet count, an increase in aspartate and alanine aminotransferase (AST and ALT) in the serum, prolongation of prothrombin and partial thromboplastin times (PT and aPTT), a fall in the fibrinogen level, an increase or decrease in the total white blood cell count, depending on the time of sample collection, and a drop in the lymphocyte count (Swanepoel et al., 1989). Circulating virus can be detected and quantitated by reverse transcriptase polymerase chain reaction (RT-PCR) (Cevik et al., 2007; Garrison et al., 2007). The level of viremia has been shown to have prognostic significance: patients with titers exceeding 10^9 genomes/mL of plasma were much more likely to die than those with lower levels; mean values for fatal cases were more than 1000-fold higher than the mean of patients who survived (Cevik et al., 2007). Viremia tends to decline with the onset of hemorrhage and shock. The development of an IgM antibody response is an early diagnostic marker seen in patients who survive, but not in fatal cases.

An unusual feature of CCHF is the occurrence of hemophagocytosis (the destruction of erythrocytes, platelets and some leukocytes by reactive histiocytes), which has been demonstrated in a number of cases by bone marrow biopsy (Cagatay et al., 2007; Fisgin et al., 2007; Karti et al., 2004). The condition is thought to be a response to the activation of monocytes by high levels of proinflammatory cytokines; its role in causing thrombocytopenia and anemia is not known.

Based on these clinical observations, the course of CCHF should be considered in four phases: incubation, prehemorrhagic, hemorrhagic, and convalescent, and effective treatment could be considered hypothetically in two phases (Fig. 1). The first starts from exposure to the virus, and is characterized by its replication and spread in the bloodstream, which usually lasts up to 15 days. In clinical terms, this period starts from the onset of prehemorrhagic symptoms (fever, myalgia, nausea and vomiting), and ends with bleeding from various sites. An antiviral drug that blocks viral replication, such as ribavirin, is most likely to be effective if initiated during this phase.

The second hypothetical phase of CCHF is characterized by the decline of viremia, but bleeding from various sites. In this phase, proinflammatory cytokines are released and the coagulation cascade is disrupted in some patients, leading to disseminated intravascular coagulation (Ergonul et al., 2006b). A drug with purely antiviral activity is less likely to be effective if begun during this phase. Although it has been suggested that ribavirin could be effective through a type of immunomodulatory activity, this has not been well documented. Alternative drugs targeted to DIC or used in sepsis could be considered in the second phase of the disease course. From this perspective, the use of corticosteroids could be studied in controlled trials during the second phase of the disease.

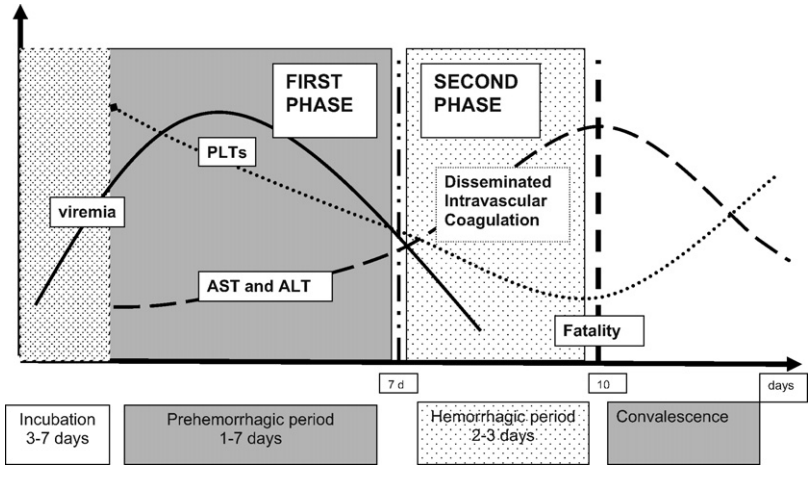

Fig. 1. Clinical stages of CCHF as they relate to therapeutic interventions (Ergonul, 2007b). Treatment could be considered in two phases. The first begins with exposure to the virus and is characterized by viremia, which usually ends within 15 days. Ribavirin is most likely to be beneficial during this phase, through its direct antiviral activity. The second is characterized by the decline of viremia and the onset of bleeding from various sites. In some patients, immunologic mechanisms such as cytokine storm disrupt the coagulation cascade and disseminated intravascular coagulation occurs. Because ribavirin is unlikely to be effective in the absence of viremia, other treatment alternatives should be considered for these patients. The only exception might be a beneficial immunomodulatory effect of ribavirin, but this remains unproven.

3. Therapy

The current approach to treatment of CCHF is based on general supportive measures, monitoring of the patient's hematologic and coagulation status, with replacement of cells and factors as needed, and the use of ribavirin. Almost all therapy has employed the oral form of the drug. An algorithm for managing a suspected case of the disease is presented in Table 1.

3.1. Ribavirin

3.1.1. Activity of ribavirin

Ribavirin (Virazole®) is a synthetic purine nucleoside analogue with a modified base and D-ribose sugar that was first synthesized by Sidwell and colleagues in 1972 (Graci and Cameron, 2006; Hayden, 2006). It inhibits the replication of a wide range of RNA and DNA viruses *in vitro*. Ribavirin was the first synthetic nucleoside to exhibit broad spectrum antiviral activity, and is still one of the few drugs in clinical use against agents other than the human immunodeficiency virus and herpesviruses (Graci and Cameron, 2006). In current clinical practice, it is used in combination with interferon-α for the treatment of hepatitis C virus infections, and in aerosol form is used to treat pediatric infection by respiratory syncytial virus (Cooper et al., 2003; Mangia et al., 2005). *In vitro* inhibitory concentrations of ribavirin may also reversibly inhibit macromolecular synthesis and proliferation of uninfected cells, suppress lymphocyte responses and alter cytokine profiles (Heagy et al., 1991). Current thoughts on the antiviral mechanism of ribavirin and information on its metabolism and toxicity are detailed in another article in this issue (Leyssen et al., 2008).

Table 1
An algorithm for managing a suspected case of CCHF

1. Suspected case
   a. Clinical symptoms (fever, myalgia, bleeding from various sites)
   b. Patient history
      i. Referral from endemic area
      ii. Outdoor activities (picnic, tracking, etc.)
      iii. History of tick exposure
      iv. Exposure to potentially viremic domestic animal blood
   c. Laboratory tests (low platelet and high white blood cell count, elevated AST, ALT, LDH, CPK)
2. Preventive measures
   a. Isolate the patient
   b. Inform and educate colleagues and staff
   c. Use barrier precautions
3. Confirmation of the case
   a. Serum for PCR (early in disease) and ELISA (late in disease or convalescence)
      i. IgM or PCR positivity confirms diagnosis, IgG cannot
      ii. Sera for differential diagnosis
4. Therapy
   a. Ribavirin
   b. Do not neglect other possible causes of the clinical picture. Starting doxycycline or equivalent should be considered
   c. Hematological support
      i. Fresh frozen plasma to improve hemostasis
      ii. Thrombocyte solutions
   d. Respiratory support
5. Follow-up and prognosis
   a. No relapse occurs after the disease, therefore there is no need for follow-up
   b. Health care workers exposed to CCHF patients or their body fluids should be followed with complete blood counts and biochemical tests for 14 days

Ribavirin is the only antiviral drug that has been used to treat viral hemorrhagic fever syndromes, including CCHF and Lassa fever (Ergonul, 2007b; McCormick et al., 1986). Viruses in the Bunyaviridae family are generally sensitive to ribavirin (Sidwell and Smee, 2003). In the only prospective, randomized, double-blind, placebo-controlled trial of ribavirin against a hemorrhagic fever virus that has been performed, ribavirin produced a significant decrease in mortality among patients with hemorrhagic fever with renal syndrome (Huggins et al., 1991). The authors concluded that early therapy had a more pronounced effect, but the window of opportunity for treatment was limited.

Ribavirin is active against CCHFV (Watts et al., 1989). Similar levels of antiviral efficacy were observed when the drug was tested *in vitro* against isolates from Nigeria, China, Uganda and South Africa (Paragas et al., 2004). In suckling mice, ribavirin treatment reduced virus growth in the liver; significantly decreased, but did not completely prevent, viremia; significantly reduced mortality; and extended the geometric mean time to death (Tignor and Hanham, 1993). The lack of other laboratory animal models of CCHF has been a major barrier to further demonstrations of drug efficacy.

The mechanism of action of ribavirin is detailed in another article in this issue (Leyssen et al., 2008), and its absorption, distribution and elimination are examined in recent reviews (Ergonul, 2007b; Hayden, 2006). No adverse event related to ribavirin therapy has yet been noted among CCHF patients, mainly for two reasons: the acute and short course of the disease, that might not allow time to development of the side effects, and overshadowing of the signs of CCHFV infection, which are the same as some potential adverse events, such as anemia. Because of the risk of teratogenic effects, the use of ribavirin is contraindicated for pregnant women.

3.1.2. Clinical use of ribavirin

No randomized clinical trials of the efficacy of ribavirin against CCHF have been performed, but its apparent efficacy has been described in several observational studies. A report published in South Africa in 1985 described the use of intravenous ribavirin for both therapy and postexposure prophylaxis in a small number of patients in a nosocomial outbreak (Van Eeden et al., 1985). The possibility of using the drug to treat CCHF did not receive wide attention until 10 years later, when Fisher-Hoch and co-workers described the use of oral ribavirin to treat three health care workers in another hospital-based outbreak (Fisher-Hoch et al., 1995). These patients were severely ill according to the severity criteria defined by Swanepoel, in which a finding of a total leukocyte count $\geq$10,000 mm^{-3}, platelet count $\leq$20,000 mm^{-3}, aspartate aminotransferase (AST) $\geq$200 U/L, alanine aminotransferase (ALT) $\geq$150 U/L, activated partial thromboplastin time (APTT) $\geq$60 s or a fibrinogen level $\leq$110 mg/dL was $\geq$90% predictive of a fatal outcome (Swanepoel et al., 1989). The

patients were started on oral ribavirin, 4 g/day in four doses for 4 days, then 2.4 g/day in four doses for 6 days. After treatment, the patients became afebrile, and their hematological and biochemical abnormalities returned to normal within 48 h. All made a complete recovery. Even though this anecdotal report did not constitute evidence of efficacy, it was encouraging, and oral ribavirin soon began to be used extensively to treat CCHFV infections. A current recommended regimen, adjusted for body weight, is 30 mg/kg as an initial loading dose, then 15 mg/kg every 6 h (4 × 1 g) for 4 days, and 7.5 mg/kg every 8 h (4 × 0.5 g) for 6 days (Ergonul, 2006).

In 2003, Mardani et al. compared the fatality rate among CCHF patients in Iran who received treatment with oral ribavirin and those who did not, using a historical control group (Mardani et al., 2003). Ninety-seven (69.8%) of 139 treated patients with suspected CCHF (based on history, examination and clinical laboratory values) and 61 (88.9%) of 69 treated patients with confirmed CCHF survived infection. By contrast, in a historical control group of 12 untreated patients with confirmed CCHF, 5 (41.7%) survived infection. The efficacy of oral ribavirin was reported to be 80% among patients with confirmed CCHF and 34% among patients suspected of having CCHF. However, in comparing treated and untreated cases, the authors did not perform a sub-group analysis to control for the severity of infection.

In 2004, we examined the effect of oral ribavirin therapy in 35 confirmed cases of CCHF in Turkey, in which we grouped the patients for analysis according to the severity of their illness (Ergonul et al., 2004). Of the 35 patients, 30 (86%) were classified as severe cases by the Swanepoel criteria. Eight were given ribavirin, and all survived, while the overall mortality among the untreated cases was 4.5%. Because the mortality in our untreated cases was much lower than the Swanepoel criteria predicted, we later revised the prognostic criteria, such that higher levels of serum AST and ALT (≥700 U/L and ≥900 U/L, respectively) were required for a case to be classified as severe (Ergonul et al., 2006a). We then used these revised criteria to analyze the efficacy of ribavirin therapy in a series of 54 patients, including the 35 in the first study. Oral ribavirin was prescribed for 22 (41%) of 45 severe cases. Three of the four fatal cases arrived at the hospital in the late stage of infection, and could not be treated with because of hematemesis. After these cases had been excluded, we found that the fatality rate was essentially the same in treated and untreated cases (Ergonul et al., 2006a). These results suggest that, given the low case fatality rate of the large number of CCHF patients that are currently being identified in Turkey, assessment of the therapeutic efficacy of ribavirin should focus on other measurable features of illness. The drug should not be thought of only as a treatment for severe cases, as such patients might be treated too late to obtain a therapeutic benefit (Ergonul, 2007b). Based on its direct antiviral activity, ribavirin is probably most useful in the early stages of the infection (Fig. 1).

The value of examining outcomes other than mortality was shown in a recent study by Ozkurt et al. (2006). The authors described the efficacy of ribavirin therapy among 60 CCHF patients in eastern Turkey, 26 of whom had a confirmed diagnosis. The mean time to clinical recovery was shorter for patients treated with ribavirin than for controls. However, there was no significant difference in fatality rates or in the need for blood and blood products, in the mean duration of hospitalization or hospital expenditure values between the two groups of patients, indicating the need for more effective treatments.

The mechanism by which ribavirin might be acting in cases of CCHF has not been determined. It is possible that the drug has an immunomodulatory effect, but this has not yet been studied. In this regard, the cytokines IL-6 and TNF-α were found to be higher among fatal CCHF patients than in nonfatal cases, whereas there was no significant difference in the levels of IL-10 between the favorable and fatal cases (Ergonul et al., 2006b). The use of corticosteroids together with ribavirin at the early stage of the infection were reported to be useful. However this experience was limited to an observational study of six patients (Jabbari et al., 2006).

3.1.3. Observational versus controlled trials

Because numerous reports have indicated that ribavirin is efficacious against CCHF, ethical considerations prevent the performance of placebo-controlled trials. Evidence of efficacy is therefore limited to observational studies, which have been criticized for their lack of randomization. However, their qualities could potentially be improved, so that they provide useful information (Vandenbroucke, 2004). Three leading confounders have made observational studies difficult to interpret.

1. *Severity of the infection*. CCHF ranges in severity from mild to severe (Ergonul, 2007a). If ribavirin is given only to the most severe cases, an observational study of mortality in treated and untreated groups would have a misclassification bias in favor of not using ribavirin, because mild cases would be unlikely to receive the drug. A well-designed study should control for the severity of treated and untreated cases to avoid misclassification bias.
2. *Number of days from onset of illness*. Some patients could receive ribavirin at an earlier, prehemorrhagic phase of the infection, whereas some may receive ribavirin treatment at a later hemorrhagic phase of the infection (Fig. 1).
3. *Severity of gastrointestinal symptoms*. Some patients cannot receive ribavirin by the oral route, because of severe hematemesis. This parameter is important in its pharmacological efficacy. Intravenous ribavirin preparations are available in some countries, and should be tried. No study has yet compared the effect of i.v. versus oral ribavirin.

If observational studies do not properly control for these variables, then misclassification bias is inevitable. In order to minimize confounders, the course of the infection should be reviewed, and the place of ribavirin in the treatment of CCHF should be detailed, based on the course of the infection.

3.1.4. Ribavirin prophylaxis following exposure to CCHFV

The value of ribavirin postexposure prophylaxis following exposure to CCHFV remains controversial (Tarantola et al., 2007). Prophylaxis is suggested after a high-risk contamina-

tion, such as a needle stick injury of a health care worker from a CCHFV infected source patient. Daily follow-up by checking complete blood count and biochemical tests for the exposed individuals is highly recommended. Ribavirin prophylaxis is generally well tolerated, potentially useful and should therefore be recommended for health care workers who are at risk of exposures such as percutaneous injuries. The dose and duration of the ribavirin prophylaxis was not detailed yet. However, oral use and the same dose and duration for the treatment are practiced (Tarantola et al., 2007).

3.2. Supportive therapy

Supportive therapy is an essential part of case management. Potential bleeding foci of the patients should be considered and preventive measures should be taken, such as use of histamine receptor blockers for peptic ulcer patients and the avoidance of intramuscular injections and aspirin or other drugs with actions on the coagulation system. Non-steroidal anti-inflammatory drugs should be avoided. Fluid and electrolyte balance should also be monitored meticulously (Ergonul, 2007b). Supportive therapy also includes the administration of thrombocytes, fresh frozen plasma (FFP), and sometimes erythrocyte preparations. The replacement therapy with these blood products should be performed by checking complete blood count, which should be done daily (Ergonul, 2006).

Thrombocyte solutions or FFP are to be used according to the deficit of the individual patient. Fatal cases of CCHF received a significantly ($p < 0.001$) higher amount of thrombocyte suspensions and FFP (Ergonul, 2007b). Sometimes, it is hard to decide where to start or stop the blood product replacement. The rules of platelet and FFP use by adapting to CCHFV infection has been described in more detail in Ergonul (2007b).

3.2.1. Platelets

Platelet transfusions should result in the prevention or resolution of bleeding caused by thrombocytopenia or platelet dysfunction. As a general rule, platelet counts should be obtained 18–24 h postinfusion. Patients who have little or no increase in the count at 18–24 h postinfusion should have counts performed 10–60 min after the next platelet transfusion. If the increment is minimal or not increased at all, the possibility of refractoriness caused by alloimmunization should be considered. Antibody-related platelet destruction is often related to the development of HLA-specific antibodies in response to foreign donor HLA antigens (Perrota et al., 2003). The patient then should be considered for HLA-matched platelet transfusions or crossmatched platelet concentrates. Poor posttransfusion platelet survival can also be seen in conjunction with fever, sepsis, disseminated intravascular coagulation, and other conditions. Patients in these settings are considered to be refractory on a nonimmunologic basis and are not expected to benefit from HLA-matched platelet transfusions (Mazza, 2002). Because disseminated intravascular coagulation occurs in the course of CCHF, some degree of platelet destruction is expected, and a rapid increase in platelet level after transfusion may not be observed.

3.2.2. Fresh frozen plasma (FFP)

FFP is plasma that is separated from whole blood and frozen within 8 h of collection, and therefore retains normal levels of clotting factors and anticoagulants. FFP is indicated to replace clotting factors in patients with demonstrated deficiencies, such as a prothrombin time or partial thromboplastin time greater than 1.5 times normal, or an international normalized ratio (INR) greater than 1.6. FFP is most commonly used in the setting of acquired coagulopathy, such as in patients with liver disease, DIC, or excess warfarin effect (Mazza, 2002). Because plasma does not contain red cells, crossmatching is not required, but the ABO type of the donor should be compatible with the recipient. The average adult dose is determined by the clinical situation and the underlying disease process. It is reasonable to administer plasma at a dose of 10–15 mL/kg of body weight (2–4 U of FFP), followed by laboratory evaluation to determine responsiveness and to decide the interval between doses. The infusion rate is determined on the basis of the patient's clinical need and hemodynamic status. FFP is thawed at 37 °C and must be transfused with 24 h of thawing if used for coagulation factor replacement. Plasma can be thawed and maintained in the refrigerated state for up to 5 days, but there is some loss of coagulation factor V and a greater decrease in factor VIII (Mazza, 2002). Treatment should result in improvement of coagulation factor deficiencies, which are assessed by the prothrombin time (INR), partial thromboplastin time, or specific factor assays (Mazza, 2002; Ergonul, 2007b).

3.3. Interferon

Type I interferon has significant antiviral activity against many hemorrhagic fever viruses *in vitro* and in animal models; however, no clinical studies have addressed the effect of interferons against CCHF (Mirazimi, 2007). Although there is no clinical benefit yet, a number of *in vitro* studies suggest that interferon treatment could have a beneficial effect. For example, MxA protein, which belongs to the dynamin superfamily of large GTPases, has antiviral activity against a wide range of viruses, including CCHFV (Andersson et al., 2004, 2006; Mirazimi, 2007). MxA colocalizes and interacts with CCHFV nucleocapsid protein in the perinuclear region of infected cells; it was therefore suggested that this interaction inhibits the virus replication process. Similar results have been observed for other bunyaviruses, suggesting that they are restricted in their intracellular growth by MxA, probably by the same mechanism (Frese et al., 1996; Kochs et al., 2002; Reichelt et al., 2004; Mirazimi, 2007).

Interferon-stimulated genes (ISGs), induced by interferon-α in human endothelial and hepatoma cells were sufficient to inhibit CCHFV growth significantly (Andersson et al., 2006). Additional proteins with potentially important antiviral activities are ISG20, P56, RNA-specific adenosine deaminase 1, promyelocytic leukemia protein and guanylate-binding protein 1 (Mirazimi, 2007). ISG20, an interferon-induced exonuclease, specifically degrades ssRNA (Espert et al., 2004). Expression of ISG20 inhibits viral replication of vesicular stomatitis virus and human immunodeficiency virus in cell culture (Espert et al., 2003, 2005). Recent studies by Weber and Mirazimi have clearly

shown that ISG20 has an antiviral activity against CCHFV by a so far unidentified mechanism (Mirazimi, 2007). Although these studies suggest that interferon treatment would be beneficial for CCHF, interferon could be induced at insufficient levels or too late in the course of infection to put MxA and other antiviral proteins in place to combat the virus when it is urgently needed (Mirazimi, 2007).

3.4. Antibody prophylaxis and treatment

Antibodies to CCHFV are typically not present within 5–9 days after the onset of illness, and patients who die of the disease do not usually develop a measurable antibody response (Papa et al., 2002; Ergonul et al., 2006a). A similar lack of antibody development among fatal cases is seen in other viral hemorrhagic fevers, such as Argentine hemorrhagic fever and Lassa fever (Enria et al., 1984). This finding encouraged the therapeutic use of antibodies derived from recovered CCHF patients or from animals. In fact, there was an early recognition of the possible benefits of treatments using serum prepared from the blood of recovered CCHF patients or gammaglobulin obtained by immunizing horses (Hoogstraal, 1979).

Bulgarian investigators reported the prompt recovery of seven severely ill patients treated via passive simultaneous transfer of two different specific immunoglobulin preparations, "CCHF-bulin" (for intramuscular use) and "CCHF-venin" (for intravenous use), prepared from the plasma of CCHF survivor donors boosted with one dose of CCHF vaccine (Vassilenko et al., 1990). No side effects were observed and the patients were discharged in good health. But because the number of the subjects was limited and the study was purely observational, further research, such as a placebo-controlled trial of immunoglobulin in addition to a standard regimen of ribavirin, will be required to assess its efficacy.

4. Vaccines

There is currently no effective vaccine available for CCHF. In the Rostov region of the former Soviet Union and in Bulgaria, an experimental vaccine was given to several hundred human volunteers, and high antibody levels were detected (reviewed in Whitehouse, 2007). No efficacy trials have been performed.

5. Future research

The fact that several hundred cases of CCHF are now being identified in Turkey every year indicates that studies of pathogenesis, rapid diagnosis and therapy that meet international ethical standards for clinical research could potentially be performed. Because a lower case fatality rate is observed in these cases than has been reported in series from other countries, indicators other than mortality should be used to evaluate treatment efficacy. These could include biochemical (severity of liver dysfunction, maximum AST level), virologic (peak viremia) and hematologic (lowest platelet count) indices and such measures of treatment efficacy as units of blood and blood products administered, the duration of illness and the length of hospital stay.

Although its apparent therapeutic efficacy precludes a placebo-controlled trial of ribavirin, it will still be possible to evaluate other therapies, such as specific immunoglobulin or corticosteroids, that are given in addition to a standard regimen of ribavirin. The relative benefit and toxicity of oral and intravenous ribavirin could also be evaluated. Development of new animal models is sorely needed to test the *in vivo* efficacy of new drugs with *in vitro* antiviral activity. In the absence of such evaluations, therapies could be tested that are already in clinical use for other diseases that are believed to have similar pathogenetic mechanisms. Agents considered in treating cases of hemophagocytosis and for the management of DIC could be useful for CCHF.

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