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Crimean-Congo Hemorrhagic Fever-Treatment and Preventive Strategies

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Crimean-Congo hemorrhagic fever is a tick-borne viral disease reported from more than 30 countries in Africa, Asia, South-East Europe, and the Middle East. The majority of human cases are workers in livestock industry, agriculture, slaughterhouses, and veterinary practice. The current mortality rate in endemic areas varies between 5 to 20 percent depending on the geographic location and medical supportive treatment. Unfortunately, there is currently no FDA-approved vaccine for prevention or specific antiviral drug for the treatment of CCHF. Ribavirin, effective against CCHFV in vitro, is one of the few options for treatment of CCHFV, but its efficacy is still questionable due to contradictory clinical studies. The efficacy of other options including Intravenous Immuneglobulin (IVIG), steroids, CCHF hyperimmuneglobulin, and CCHF monoclonal antibodies is still controversial.

Keywords: Hemorrhagic Fever, Crimean; Therapeutics; prevention and Control

1. Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne disease caused by a nairovirus (family Bunyaviridae). Crimean-Congo hemorrhagic fever virus (CCHFV) is endemic/enzootic in several countries in Africa, Asia, Europe, and the Middle East. The disease was first described in the Crimea in 1944 and given the name Crimean hemorrhagic fever. In 1969, it was recognized that the same pathogen was responsible for an illness identified in 1956 in the Congo; linkage of the two place names resulted in the current designation of Crimean-Congo hemorrhagic fever virus (CCHFV). CCHF patients may develop either a mild, nonspecific febrile syndrome or a more severe illness with vascular leak, hemorrhage and shock. Most cases occur sporadically, as a result of tick bite or direct contact with the blood or tissues of an infected animal.

2. Prevention of CCHF

Between 1969 and 1970, researchers of the Soviet Institute of Poliomyelitis and viral encephalitides developed an experimental vaccine based on brain tissue from CCHFV-infected newborn laboratory white mice and newborn albino rats. Brain tissue suspensions were inactivated by formaldehyde and heat treatment to obtain safe and non-infectious preparations. The vaccine did not have adverse affects on a limited number of humans who volunteered to be vaccinated with the preparation. Finally, in 1970, this inactivated anti-CCHF vaccine was approved by the Soviet Ministry of Health for CCHFV prophylaxis (1).

In 1974, this vaccine was licensed in Bulgaria and used in CCHFV-endemic parts of the country for persons over 16 years of age, such as military personnel or medical and agricultural workers. Recently published data from the Bulgarian Ministry of Health suggest a four-fold reduction in the number of reported CCHF cases over a 22-year time period (1953-1974: 1105 cases; 1975-1996: 279 cases) (2).

Modern vaccine development foresees the establishment of DNA vaccines, recombinant virus proteins-based vaccines, and virus-like particle (VLP) vaccines. For instance, American scientists have attempted to develop a CCHF DNA vaccine and tested its immunogenicity in mice. The DNA vaccine contained the entire M segment coding region of the CCHFV genome and elicited neutralizing antibodies in some of the vaccinated mice, as well as antibodies that co-immunoprecipitated the radiolabeled CCHFV M segment expression products (3).

3. Treatment

There is currently no specific treatment for CCHFV and therefore care of patients relies on active supportive clinical management, anti-CCHF hyperimmune sera, and the administration of ribavirin.

3.1. Ribavirin

The results of the available studies are at best confusing (Table 1, studies numbered 4-23) (4-23). There has been too much underlying variations in patient populations of different studies to draw any definite conclusion regarding the efficacy of ribavirin. It seems that treatment with ribavirin early in the course of infection may be ben-

eficial. This approach to treating CCHF patients has been practiced in Middle Eastern countries for several years. A definite confirmation of ribavirin efficacy still requires better designed clinical trials, including studies with larger patient cohorts with matched controls in terms of confounding factors such as additional supportive treatments that can influence the disease outcome. One of the problems is the ethical issue regarding negative controls. On one hand, negative controls (i.e. untreated patients suffering from CCHF) are required to adequately judge the efficacy of a drug such as ribavirin in a patient cohort. On the other hand, CCHF is a readily fatal disease and it is clearly unethical to withhold a potentially effective treatment from an ailing patient. Additionally, CCHFV is a rather sporadic disease and larger outbreaks of the disease cannot easily be predicted. Setting up large clinical trials takes time and is logistically challenging. Designing them in the absence of knowledge regarding the whereabouts and extent of a CCHF outbreak is daunting. It is also unlikely that the burden of a larger, well-controlled and internationally acceptable CCHF clinical trial can be carried by a single country or region. A close interaction between all scientists in a CCHFV-endemic region with scientists all over the world and exchanging their expertise and resources would be most beneficial. However, whereas the bon mot "think globally not locally" sounds like a good summary on how to move forward one should not forget that numerous political and religious tensions exist among important countries that experience CCHF and those that could provide logistics, funding, and additional scientific expertise. How to uncouple humanitarian aid in crisis areas from global politics unfortunately remains an unsolved challenge and is one that must stand at the forefront of problems to be solved to control diseases such as CCHF.

In summary although there is no confirmation for the clinical efficacy of ribavirin, given the safety of short term ribavirin treatment and high case-fatality rate of CCHF, it is probably justifiable to initiate ribavirin treatment of all suspected cases in an endemic area until the accumulation of better (supporting or non-supporting) data for this particular treatment.

3.2. Anti-CCHF Immunoglobulin

None of the studies described above have proven the efficacy of immune serum in post-exposure prophylaxis or treatment of CCHF. Just as in the case of ribavirin, immune sera have to be further evaluated in better designed clinical trials. For instance, one patient group could receive ribavirin and a control group could receive

Table 1. Summary of Literature Published since 1985 until 2010 on the Efficacy of Ribavirin in CCHF

Studies, No	Country	Number of Treated Cases/Total Number of Cases	Study Type	Ribavirin Used as Treatment or Prophylaxis	Reference
1	South Africa	6/9	Observational	Prophylaxis	(7)
2	Pakistan	3/3	Observational	Treatment	(4)
3	Pakistan	2/2	Observational	Treatment	(5)
4	Pakistan	12/12	Observational	Prophylaxis in 11 cases	(6)
5	Pakistan	9/9	Observational	Treatment	(8)
6	Iran	6/6	Observational	Treatment	(9)
7	Turkey	10/10	Observational	Treatment	(10)
8	Turkey	235/281	Observational	Treatment	(6)
9	Iran	236/255	Historical comparison	Treatment	(11)
10	Iran	61/69	Historical comparison	Treatment	(12)
11	Turkey	22/60	Historical comparison	Treatment	(13)
12	Turkey	126/218	Historical comparison	Treatment	(14)
13	Turkey	8/30	Non-randomized clinical trial	Treatment	(15)
14	Turkey	9/25	Non-randomized clinical trial	Treatment	(16)
15	Turkey	41/52	Non-randomized clinical trial	Treatment	(17)
16	Iran	184/184	Comparison to evaluate timing	Treatment	(18)
17	Iran	63/63	Comparison to evaluate timing	Treatment	(19)
18	Iran	155/155	Comparison to evaluate timing	Treatment	(20)
19	Turkey	64/136	Randomized clinical trial	Treatment	(21)

ribavirin plus immune sera. Ethical issues would not ensue as ribavirin would be administered to both groups. It seems that a collaborative study between countries that have enough supplies of immune sera, such as Bulgaria, and those that experience a higher incidence rate of CCHF (such as Turkey or Iran) could address the issue of efficacy of immune sera. A different way forward for countries with a higher incidence rate of CCHF would be to prepare large stocks of immune sera from affected patients and evaluate them during a subsequent outbreak.

3.3. Anti-CCHF Monoclonal Antibodies

Monoclonal antibodies were first used for CCHFV identification in 1987 (24). Serum therapy for treatment or prophylaxis of CCHF has been used since 1964 (25). Scientists are now attempting to develop anti-CCHFV specific monoclonal antibodies (mAbs) for the treatment of patients. Monoclonal antibodies specific to both the CCHF Gn and Gc surface glycoproteins were generated to evaluate their neutralization and protective properties (26). It was concluded that neutralization of CCHFV depends not only on the properties of the used antibody, but also on host factors and non-neutralizing antibody-dependent mechanisms, such as antibody-dependent cell-mediated cytotoxicity.

3.4. Intravenous Immuneglobulin (IVIG)

There is little supporting the use of IVIG in treatment of patients with CCHF. In a recently published article from Iran, IVIG plus ribavirin were effective in reducing time to normalization of white blood cells (WBC), liver functions tests and platelet count in 12 patients compared to 28 patients who only received ribavirin. IVIG was not effective to reduce mortality which can be related to low number of cases in this study (22). In another study from Turkey, IVIG in association with high dose methylprednisolone was effective to decrease time to normalization of WBC, platelet count and D-dimer levels in 12 CCHF patients with reactive hemophagocytichistiocytosis (27). There is no more data available on this subject and more studies are needed for better evaluation.

3.5. Steroids

Role of high dose steroids has been studied in only one clinical trial in Iran(28), though it has been evaluated in other studies in Turkey (29). In the Iranian study, high dose methylprednisolone was tried in 13 patients with severe thrombocytopenia at presentation and results were compared to 22 patients with the same presentation. The result showed that treatment group had faster recovery in platelet and WBC counts compared to controls (28).

Both Iranian and Turkish studies showed better outcome and decreased mortality in patients with severe CCHF. These data support the usage of high dose corticosteroid in severely ill patients but more studies are needed to evaluate this effect better.

4. Summary

In conclusion, the only available and probably somewhat efficacious CCHF vaccine is an inactivated antigen preparation that is currently used in Bulgaria. DNA vaccines, recombinant CCHFV proteins, and CCHFV-like particles (VLPs) are promising candidates to be used in developing novel vaccines. However, given the overall scarcity of CCHF even in endemic countries it is questionable that large vaccination trials could be performed in human populations. This includes the problem of finding volunteers for vaccination, which is a task not to be easily neglected given the growing resistance of educated populations against using vaccines protecting them from dangerous and contagious diseases such as measles or poliomyelitis. Nobody has yet answered the question on how many people would have to be vaccinated and for how long they would have to be followed to conclude that a given vaccine is protective. Most scientists therefore believe in treatment rather than prophylaxis and think that ribavirin may be an effective treatment for CCHF, but some recently conducted and well-designed clinical trials counterprove this assumption. Immunoglobulin preparations (CCHF-bulin and CCHF-venin) have been used in Bulgaria for quite some time but no new data on these preparations have been published since 1990 and the confirmation of their efficacy requires additional studies. Current developments in antibody engineering have raised hopes for novel preventive and treatment strategies for CCHF, but there is currently no human monoclonal anti-CCHFV antibody available. At this point, all hopes for treatment depend on the development of two novel mouse models for CCHF. Immune sera, antibodies, ribavirin and more novel ways of treatment could at least theoretically be evaluated in these models and allow to draw some firm conclusions regarding their value.

References

1. Tkachenko YA, Butenko AM, Butenko SA, Zavodova TI editors. Prophylactic characteristics of a protective Crimean hemorrhagic fever vaccine, in: Chumakov. In: *Crimean hemorrhagic fever Materials of the 3rd scientific-practical conference*. 1970 Rostov-na-Donu. USSR: pp. 136–8.
2. Christova I, Kovacheva T, Georgieva D, Ivanova S, Argirov D. Congo-Crimean haemorrhagic fever virus - Bulgarian input in fighting the disease. *Probl. Infect. Paras. Dis.* 2009;**37**:7–8.
3. Spik K, Shurtleff A, McElroy AK, Guttieri MC, Hooper JW, Schmaljohn C. Immunogenicity of combination DNA vaccines for Rift Valley fever virus, tick-borne encephalitis virus, Hantaan virus, and Crimean Congo hemorrhagic fever virus. *Vaccine*. 2006;**24**(21):4657–66.
4. Fisher-Hoch SP, Rehman S, Khan JA, Mirza S, Khurshid M, McCormick JB. Crimean Congo-Haemorrhagic Fever treated with oral ribavirin. *Lancet*. 1995;**346**(8973):472–5.
5. Athar MN, Baqai HZ, Ahmad M, Khalid MA, Bashir N, Ahmad AM, et al. Short report: Crimean-Congo hemorrhagic fever outbreak in Rawalpindi, Pakistan, February 2002. *Am J Trop Med Hyg*. 2003;**69**(3):284–7.
6. Bangash SA, Khan EA. Treatment and prophylaxis with ribavirin for Crimean-Congo Hemorrhagic Fever--is it effective? *J Pak Med Assoc*. 2003;**53**(1):39–41.
7. van de Wal BW, Joubert JR, van Eeden PJ, King JB. A nosocomial outbreak of Crimean-Congo haemorrhagic fever at Tygerberg

Hospital. Part IV. Preventive and prophylactic measures. *S Afr Med J*. 1985;**68**(10):729–32.
8. Smego RJ, Sarwari AR, Siddiqui AR. Crimean-Congo hemorrhagic fever: prevention and control limitations in a resource-poor country. *Clin Infect Dis*. 2004;**38**(12):1731–5.
9. Jabbari A, Besharat S, Abbasi A, Moradi A, Kalavi K. Crimean-Congo hemorrhagic fever: case series from a medical center in Golestan province, Northeast of Iran (2004). *Indian J Med Sci*. 2006;**60**(8):327–9.
10. Midilli K, Gargili A, Ergonul O, Sengoz G, Ozturk R, Bakar M, et al. Imported Crimean-Congo hemorrhagic fever cases in Istanbul. *BMC Infect Dis*. 2007;**7**:54.
11. Alavi-Naini R, Moghtaderi A, Koohpayeh HR, Sharifi-Mood B, Naderi M, Metanat M, et al. Crimean-Congo hemorrhagic fever in Southeast of Iran. *J Infect*. 2006;**52**(5):378–82.
12. Mardani M, Jahromi MK, Naieni KH, Zeinali M. The efficacy of oral ribavirin in the treatment of crimean-congo hemorrhagic fever in Iran. *Clin Infect Dis*. 2003;**36**(12):1613–8.
13. Ozkurt Z, Kiki I, Erol S, Erdem F, Yilmaz N, Parlak M, et al. Crimean-Congo hemorrhagic fever in Eastern Turkey: clinical features, risk factors and efficacy of ribavirin therapy. *J Infect*. 2006;**52**(3):207–15.
14. Elaldi N, Bodur H, Ascioglu S, Celikbas A, Ozkurt Z, Vahaboglu H, et al. Efficacy of oral ribavirin treatment in Crimean-Congo haemorrhagic fever: a quasi-experimental study from Turkey. *J Infect*. 2009;**58**(3):238–44.
15. Ergonul O, Celikbas A, Dokuzoguz B, Eren S, Baykam N, Esener H. Characteristics of patients with Crimean-Congo hemorrhagic fever in a recent outbreak in Turkey and impact of oral ribavirin therapy. *Clin Infect Dis*. 2004;**39**(2):284–7.
16. Cevik MA, Elaldi N, Akinci E, Onguru P, Erbay A, Buzgan T, et al. A preliminary study to evaluate the effect of intravenous ribavirin treatment on survival rates in Crimean-Congo hemorrhagic fever. *J Infect*. 2008;**57**(4):350–1.
17. Tasdelen Fisgin N, Ergonul O, Doganci L, Tulek N. The role of ribavirin in the therapy of Crimean-Congo hemorrhagic fever: early use is promising. *Eur J Clin Microbiol Infect Dis*. 2009;**28**(8):929–33.
18. Metanat M, Sharifi-Mood B, Salehi M, Alavi-Naini R. Clinical Outcomes in Crimean-Congo Hemorrhagic Fever: A Five-years Experience in the Treatment of Patients in Oral Ribavirin. *Int J Virol*. 2006;**2**(1):21–4.
19. Izadi S, Salehi M. Evaluation of the efficacy of ribavirin therapy on survival of Crimean-Congo hemorrhagic fever patients: a case-control study. *Jpn J Infect Dis*. 2009;**62**(1):11–5.
20. Sharifi-Mood B, Metanat M, Ghorbani-Vaghei A, Fayyaz-Jahani F, Akrami E. The outcome of patients with Crimean-Congo hemorrhagic fever in Zahedan, southeast of Iran: a comparative study. *Arch Iran Med*. 2009;**12**(2):151–3.
21. Koksal I, Yilmaz G, Aksoy F, Aydin H, Yavuz I, Iskender S, et al. The efficacy of ribavirin in the treatment of Crimean-Congo hemorrhagic fever in Eastern Black Sea region in Turkey. *J Clin Virol*. 2010;**47**(1):65–8.
22. Keshtkar-Jahromi M, Kuhn JH, Christova I, Bradfute SB, Jahrling PB, Bavari S. Crimean-Congo hemorrhagic fever: current and future prospects of vaccines and therapies. *Antiviral Res*. 2011;**90**(2):85–92.
23. Salehi H, Salehi M, Adibi N, Salehi M. Comparative study between Ribavirin and Ribavirin plus Intravenous Immunoglobulin against Crimean Congo hemorrhagic fever. *J Res Med Sci*. 2013;**18**(6):497–500.
24. Blackburn NK, Besselaar TG, Shepherd AJ, Swanepoel R. Preparation and use of monoclonal antibodies for identifying Crimean-Congo hemorrhagic fever virus. *Am J Trop Med Hyg*. 1987;**37**(2):392–7.
25. Lazarev VN. Treatment of Crimean hemorrhagic fever patients with convalescent sera. In: Chumakov MP editor. *Arboviruses (Tick-borne and Japanese encephalitides, hemorrhagic fevers, and other arboviral infections)*.. Moscow, USSR: Materials of the 16th scientific session of the Institute of Poliomyelitis and Viral Encephalitides,; 1969. pp. 142–3.
26. Bertolotti-Ciarlet A, Smith J, Strecker K, Paragas J, Altamura LA, McFalls JM, et al. Cellular localization and antigenic characterization of crimean-congo hemorrhagic fever virus glycoproteins. *J Virol*. 2005;**79**(10):6152–61.
27. Erduran E, Bahadir A, Palanci N, Gedik Y. The treatment of crimean-congo hemorrhagic fever with high-dose methylprednisolone, intravenous immunoglobulin, and fresh frozen plasma. *J Pediatr Hematol Oncol*. 2013;**35**(1):e19–24.
28. Sharifi-Mood B, Alavi-Naini R, Metanat M, Mohammadi M, Shakeri A, Amjadi A. Efficacy of high-dose methylprednisolone in patients with Crimean-Congo haemorrhagic fever and severe thrombocytopenia. *Trop Doct*. 2013;**43**(2):49–53.
29. Dilber E, Cakir M, Erduran E, Koksal I, Bahat E, Mutlu M, et al. High-dose methylprednisolone in children with Crimean-Congo haemorrhagic fever. *Trop Doct*. 2010;**40**(1):27–30.