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Therapeutic Options for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) – possible lessons from a systematic review of SARS-CoV therapy

Hisham Momattin [a], Khurram Mohammed [a], Alimuddin Zumla [b], Ziad A. Memish [c], Jaffar A. Al-Tawfiq [d,*]

[a] Pharmacy Services Division, Saudi Aramco Medical Services Organization, Dhahran, Saudi Arabia
[b] Division of Infection and Immunity, University College London, London, and University College London Hospitals NHS Foundation Trust
[c] Deputy Minister for Public Health, and Director WHO Collaborating Center for Mass Gathering Medicine Ministry of Health, and Professor, Al-Faisal University, Riyadh, Saudi Arabia
[d] Specialty Internal Medicine, Saudi Aramco Medical Services Organization, Dhahran, Saudi Arabia, and Indiana University School of Medicine, Indiana, USA

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ABSTRACT

The Middle East Respiratory Syndrome coronavirus (MERS-CoV) has been detected in a number of countries in the Middle East and Europe with an apparently high mortality rate. It is phylogenetically related to the SARS coronavirus and has also been associated with severe respiratory illness as well as nosocomial transmission in healthcare settings. Current international recommendations do not support any specific therapies; however, there are a number of agents, which were used during the SARS epidemic of 2003. It is possible that these might be active against the related MERS coronavirus. We have reviewed the literature on the safety and efficacy of therapies used in patients with SARS with a view to their potential use in patients with MERS-CoV infections.

1. Introduction

Coronaviruses are RNA viruses which usually cause mild upper respiratory illnesses. The emergence of SARS (severe acute respiratory Syndrome) MERS (Middle east respiratory syndrome) has focussed global attention on the clinical significance of cornaviruses.

The current Middle East Respiratory Syndrome Novel coronavirus (MERS-CoV) was first isolated in June 2012 from the respiratory tract of a businessman in the Bisha area of Saudi Arabia, who subsequently died of pneumonia and renal failure.[1] As of 28 July 2013 MERS-CoV has caused 91 laboratory confirmed cases and 46 deaths, representing a high case fatality rate of 50%.[2] The high case fatality rate is likely related to the pattern of the disease as we probably are seeing only the tip of the iceberg of critically ill and admitted patients. The high fatality rate is likely to decline as milder clinical cases emerge. Similar to SARS, common symptoms in patients with MERS-CoV include fever, cough, shortness of breath, and gastrointestinal symptoms. Most patients have had pneumonia and the majority was reported to have multiple co-morbid conditions.[3,4]

The rapid deployment of effective therapeutics is a high priority as there is currently no specific therapy or vaccine for MERS-CoV. The clinical experience from SARS suggests that a number of interventions including ribavirin with and without corticosteroids, interferon alfa with corticosteroids, ribavirin with lopinavir and ritonavir, and convalescent plasma may improve the outcome in patients but the data are not conclusive.[5]

The purpose of this review is first to summarize the effectiveness of these treatments, in an attempt to identify a therapeutic approach that could help select the most appropriate therapeutic options for patients with MERS-CoV infections.

2. Methods

We systematically searched the literature databases (PubMed, Science Direct and the Cochrane database) for published studies. We used the key words "SARS", "coronavirus", in combination with "treatment", human studies, randomized controlled trials (RCT), prospective *or* retrospective cohort designs, case-control designs,

* Corresponding author. P.O. Box 76, Room A-428-2, Building 61, Dhahran Health Center, Saudi Aramco, Dhahran 31311, Saudi Arabia. Tel.: +966 3 877 3524; fax: +966 3 877 3790.
E-mail addresses: jaffar.tawfiq@aramco.com, jaltawfi@yahoo.com (J.A. Al-Tawfiq).

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Table 1
Summary of Ribavarin Therapy in the treatment of SARS patients

Reference #	Type of study	Dose	# patients	Time of administration	Outcome
8	Observational (LOE, III)	IV loading dose 2g then 1 g IV q6h x 4 days then 500 mg IV Q8h x 4-6 days	7	Upon admission to a medical ward	**Outcome** **N=7** Died 2 Improved within 5 days 5 - Recovered completely 3 - mild dyspnea with 3 weeks follow-up 2
9	Observational (LOE, III)	9 patients on 8mg/kg IV q8H 1 patient on 1.2 g po Q8h (Duration of therapy not mentioned)	10	Upon admission	Inconclusive **Outcome** **N=10** Died with respiratory failure 2 Resolution of fever and improvement in heart rate within 2 days 8 Recovered completely 1 Able to walk on the level without apparent restriction 4 Able to walk 3-5 steps on the level 3 Mild dry cough 4
10	Retrospective case series (LOE, II)	Loading dose of 2 g IV, then 1 g IV q6h for 4d, then 500 mg q8h for 3d The median treatment was 6d. 40% received steroids; Most patients received approximately 20 to 50 mg/d of hydrocortisone for 10 days. One patient received pulse steroid.	111	91% started on ribavirin within the first 48hr of hospitalization. <20% received steroid in the first 48 hours.	Ribavirin was associated with significant toxicity **Ribavirin toxicity** **N= 111** Hemolysis (%) 76 Decrease in hemoglobin of 2 g/dL (%) 49 Admitted to the ICU (%) 20 21-day mortality 6.5% Possible harm
11	Retrospective cohort study (LOE,II)	PO 20 mg/kg TID **versus** Oseltamivir, 75 mg BID	Ribavirin (n= 14) Oseltamivir (n=6)	Most of patients at day 10-14 of symptoms.	**Outcome** **Oseltamivir N=6** **Ribavirin N=14** improved sufficiently to be extubated 2 0 required mechanical ventilation 0 6 died of progressive respiratory failure 0 3 Inconclusive There is no obvious response to ribavirin, and several patients deteriorated in spite of its use. In contrast, a number of patients recovered without use of ribavirin.
12	Prospective observational study (LOE, II)	IV 8mg/kg Q8h for 14days + hydrocortisone 200 mg IV Q8 h over 10 days, then PO prednisolone 1mg/kg for 5 days, 0·5 mg/kg for 3 days, and 0·25 mg/kg for 3 days. pulses of methylprednisolone 500 mg IV OD for 2-3 doses	75	After diagnosis of SARS	Worsening in week 2 is unrelated to uncontrolled viral replication but may be related to immunopathological damage. **Outcome** Death* 5 (7%) Convalescence at home or at rehabilitation facility 27 (36%) Hospital admission 29 In general ward (39%) In intensive-care unit for ARDS 13 (17%) *Two patients died of acute myocardial infarction, one of clinical sepsis, and two of clinical sepsis and ARDS **Inconclusive**

13	Randomized control trial (LOE,II2)	190 patients A (40) B (30) C (60) D (60) ribavirin IV interferon-alpha IM: No / Yes / Some / 45 patient Antibiotics: C-S / AZ, FQ / AZ, FQ / AZ, LF AZ =azithromycin, FQ =quinolone; LF = levofloxacin Steroids were added (methyl prednisolone 80–160 mg OD for 2–3 days) when symptoms worsened. In group D few patients received high dose methylprednisolone up to 1000 mg/daily	At the time of admission	Factor / A / B / C / D Resolution of pyrexia (days): 9.4 ± 3.6 / 6.7 ± 1.9 / 7.2 ± 2.8 / 3 ± 1.4 Respiratory improvement (days): 10.9 ± 7.3 / 9.8 ± 5.1 / 7.8 ± 3.9 / 5.9 ± 2.6 require mechanical ventilation: 3 / 2 / 8 / 0 Deaths: 2 / 2 / 7 / 0 Resolution of pyrexia and respiratory improvement was significantly better in group D (p> 0.05)
14	Prospective cohort study (LOE, II)	**156 patients** cefotaxime + PO levofloxacin or clarithromycin + Oseltamivir **or** PO ribavirin loading dose 2.4 g then 1.2 g TID + prednisolone 0.5–1 mg/kg/day), patient with dyspnea were treated with IV ribavirin 400 mg Q8h + hydrocortisone 100 mg Q8h). **or** Pulses of methylprednisolone 0.5 g IV infusion for 3 days.	After 48h of persistent fever	Broad spectrum antimicrobial (n = 138) / Ribavirin + steroid (n = 138) / methylprednisolone` IV (n = 107) Sustained response: 0 (0) / 16 (11.6%) / 50 (46.7%) Partial response: 0 (0) / 9 (6.5%) / 45 (42.1%) No response: 138 (100%) / 113 (81.9%) / 12 (11.2%) Possible harm
15	Retrospective (LOE II)	**40 patients** Treatment consisted of Ribavarin with either intravenous or oral hydrocortisone with or without one pulsed steroid regime (intravenous methylprednisolone 500 mg per day for 3–5 days)	mean time of 3.4 days ± 3.6 (median, 2 days; range, 1–19 days) after admission	Inconclusive. There was no mention of the total number of respondents. It is rather surprising that patients with long treatment delay had a good response. This is partly related to that the allocation to different regimens was not randomized and the criteria not described in the paper. Parameters that influenced treatment response were time from symptom onset to treatment day (P=0.003), time from admission to treatment day (P=0.001), time to maximal radiographic score from treatment day (P=0 .001), maximal radiographic score (P=0.009), SaO2 at maximal radiographic score (P= 0.13).
16	retrospective cohort study (LOE, II)	**229patients** **(97 ribavirin)** PO1.2 g TID or IV 400 mg Q8h **Versus** no treatment	at a mean of 6.4 days of illness	Use of ribavirin did not confer any benefit for patients with SARS. Outcome / Non-ribavirin (%, n = 132) / Ribavirin (%, n = 97) / P-value Number of death (%): 17 (12.9) / 10 (10.3) / 0.679 Number of ever admitted to ICU (%): 27 (20.5) / 19 (19.6) / >0.999

or case series; agents included were ribavirin, interferon, Lopinavir and ritonavir (LPV/r), and convalescent plasma. We exclude corticosteroid studies as this was beyond the scope of this review and the management of severe pneumonia has been well covered in the WHO guideline.[6]

Data extracted from these publications include: authors name, publication year, type of study, level of evidence, sample size, interventions dose, duration, indication, route, and time of administration, number of patients, and efficacy and safety outcome of these interventions. The outcomes of interest included mortality rate, measures of morbidity and adverse effects. The outcomes reported in the selected studies included death, mechanical ventilation, improvement of symptoms, admission to the intensive care unit, infectious complications, successful discharge and adverse effects.

3. Assessment of study quality

The clinical studies were all critically appraised. Aspects that were assessed included study design, the possibility of bias in the selection of the control group and treatment allocation, and whether the treatment regimen and reporting of outcomes were consistent. The studies were tabulated and summarized in a narrative way, and were grouped by the treatment strategy. We categorized each article depending on which drug was used. We tabulated results as type of study, dose, duration, time of administration, and indication of medication, number of patients included in that study, plus the final outcomes.

The studies were scored using the US Preventive Services Task Force scoring system[7], where Level of Evidence.

LOE, I: Evidence obtained from at least one properly designed randomized controlled trial.
Level II-1: Evidence obtained from well-designed controlled trials without randomization.
Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

4. Results

We identified 54 studies about SARS or coronavirus and we included 19 studies only. We excluded 35 studies since 14 of them were in vitro studies, 15 corticosteroid studies, and 6 were non-therapeutic studies. Overall, we analyzed 19 studies, nine used ribavirin alone or with interferon (Table 1)[8–16], two used lopinavir and ritonavir (Table 2)[17,18], six used convalescent plasma (Table 3)[19–22], there was one study of Interferon alpha (Table 4)[23] and one study comparing Interferon alpha versus ribavirin[13]. Summaries of the different studies are presented in Tables 1–4.

Table 2
Lopinavir/Ritonavir studies

Reference #	Type of study	Regimen	# patients	Indication	Time of administration	Outcome
17	Cohort study (LOE, II)	Ribavirin for 10-14days (2.4 g PO loading dose, followed by 1.2 g PO Q8h, or 8 mg/kg IV Q8h, if the patient could not tolerate oral treatment), + corticosteroid therapy for 21 days (hydrocortisone 100-200 mg Q 6-8 hours, or methylprednisolone 3 mg/kg/day, depending on severity) If no response pulses of methylprednisolone 500-1000 mg IV OD were used as rescue therapy, then + lopinavir 400 mg/ritonavir 100 mg PO Q12h for 10 to 14 days	1052 patients	SARS	In newly diagnosed patient; or as rescue therapy later in the course of the illness when patients had worsening symptoms	The addition of lopinavir/ritonavir to a standard treatment protocol as an initial treatment appeared to be associated with improved clinical outcome and reduce death rate The addition of lopinavir/ritonavir to a standard treatment protocol As a rescue for SARS no clinical improvement. The authors report a significant effect ($p<0.05$) on death rate,ventilater rater rates and proportion requiring methylprednisolone pulse **LPV/r, n=44** / **cohort, n=634** Death rate (%) 2.3 / 15.6 Intubation rate (%) 0 / 11 Desaturation rate (%) 68.2 / 84.5 Proportion requiring pulse methylprdnisone (%) 27.3 / 55.4 Mean pulse methylprednisolone dose (G) 1.6 / 3.0
18	Cohort (LOE, II)	Historical group: Ribavirin for 14 days (4 g PO loading dose followed by 1.2 g Q8h, or 8 mg/kg IV Q8h + corticosteroid for 21 days (starting dose: hydrocortisone 100–200 mg Q 6–8 hours or methylprednisolone 3 mg/kg/day). Pulses of IV methylprednisolone (0.5–1 g/day up to 4 g) if needed Treatment group: + lopinavir (400 mg)/ritonavir (100 mg) PO Q12h for 14 days	41 patients treated, 111 Historical (152)	SARS	Newly diagnosed SARS patients with no ARDS	Patients treated with lopinavir/ritonavir appeared to run a milder disease course in terms of diarrhea, recurrence of fever, and worsening of chest radiographs. A reduction in the viral load, reduction in steroid usage and nosocomial infections was seen in patients initially treated with lopinavir/ritonavir Historical controls (n = 111) / Treatment group (n = 41) / p value Development of ARDS or death within 21 days 32 (28.8%) / 1 (2.4%) / <0.001 Death/ARDS at day 21 7 (6.3%)/25 (22.5 / %) 0 (0%)/1 (2.4%) / -

Table 3
Convalescent Plasma studies

Reference #	Type of study	Regimen	# patients	Indication	Time of administration	Outcome
19	Cohort study (LOE,II)	Convalescent plasma (500 mL) was obtained from each of three SARS patients and transfusedinto the 3 infected HCW.	3 patients	SARS	No date was given	All three patients survived. One healthcare worker became pregnant subsequently, delivering 13 months after discharge.
20	Case report (LOE, III)	infusion of plasma collected (200ml) from a convalescent patient with SARS to treat, in combination with ribavirin and corticosteroids	One patient	SARS	On day 14 of hospitalization	The clinical outcome was successful, despite the relatively low volume of plasma infused; furthermore, no side-effects were observed
21	Cohort (LOE, II)	200-400ml (4-5ml/kg) of |ABO compatible convalescent plasma	80 patients		On day 14 of starting symptoms	Mortality rate 12.5% compared to 17% of SARS patient
22	Retrospective cohort study (LOE, II)	ribavirin + methylprednisolone 3 doses (500 mg each) of pulsed methylprednisolone 200-400 ml of convalescent plasma (plasma group) or further pulses of methylprednisolone (steroid group) 200–400 mL of	30	SARS	At the discretion of theattending clinicians and according to the availability of convalescent plasma.	Plasma group (n= 19) / Steroid group (n= 21) / P value Discharge rate by day 22 Following onset of illness: 73.4% N= 14 / 19% N= 4 / 0.001 Discharge rate by day 22 after adjustment for co-morbidities: 77.8% (14/18) / 23% (3/13) / 0.004 Death rate: 0% / 23.8% (n=5) / 0.049 Inconclusive

Table 4
Interferon alpha studies

Reference #	Type of study	Regimen	# patients	Indication	Time of administration	Outcome
23	Retrospective cohort study (LOE,II)	Prednisone PO 50mg BID or IV methylprednisolone 40mg Q12h if not control IV methylprednisolone 500mg OD for 3 days then taper and step down to PO prednisone to complete 20days SQ interferon alfacone-1 for 10 days starting with 9mcg/d for at least 2 days then 15 mcg/d if no response for 8-13 days	28	SARS	When health Canada approval for interferon alfacone-1 use in SARS treatment (may 29, 2003)	Resolution of fever and lymphopenia were similar between groups corticosteroids alone (n= 13) / interferon alfacon-1 (9) transferred to the intensive care unit: 5 (38.5%) / 3 (33.3%) required intubation and mechanical ventilation: 3 (23.1%) / 1 (11.1%) died: 1 (7.7%) / 0 (0%) The interferon alfacon-1 treatment group had a shorter time to 50% resolution of lung radiographic abnormalities (P =.001), had better oxygen saturation (P =.02), resolved their need for supplemental oxygen more rapidly (P =.02), had less of an increase in creatine kinase levels (P =.03), and showed a trend toward more rapid resolution of lactate dehydrogenase levels compared with the group receiving corticosteroids alone. Inconclusive

5. Discussion

There has been a lot of concern worldwide about the emergence of the MERS-CoV. Although infection control, molecular diagnostics and international public health have improved considerably since the 2003 SARS epidemic, there are still no proven or licensed therapies for any coronavirus infection. The high mortality associated with MERS-CoV led us to conduct this systematic review to summarize the available options for treatment for novel coronavirus infection based on previous reports of therapy of SARS, a related coronavirus.

The most commonly used agent was the broad spectrum antiviral ribavirin. There were seven reports of the use of ribavirin in SARS patients although only four reported control groups. The mortality benefit was inconsistent with mortality rates of between 5% and 42.8%,[8–14] two studies showed improvements of symptoms in 71.4%-80% of patients, and ICU admission rates of 13%-20%.[8,9] The major problem with ribavirin was the significant incidence of adverse events especially hemolysis which was reported in 68.5%.[10]

The timing of the start of antiviral agents is important in most virus infections. One study compared oseltamivir versus ribavirin and showed no obvious response to ribavirin, however, the treatment were started after 10-14 days of symptoms which might have led to the poorer outcomes.[11]

There was only one randomized controlled trial: this compared ribavirin versus interferon-1α and showed no advantage of ribavirin over interferon in patients with SARS.[13] In addition, there were observational studies comparing Interferon-1α with untreated controls.[23] Interferon led to improvements in clinical and laboratory parameters compared with control patients.[23] However, there was no standard regime used and adverse events were not well documented.

The addition of lopinavir/ritonavir to ribavirin regimen was associated with improved clinical outcome and reduces the death rate comparing to ribavirin regimen alone in observational studies.[17,18] These studies are detailed in Table 2.

Few studies addressed the effect of convalescent plasma.[19–22] These studies were mainly case reports which limit the generalizability of their findings. In three studies of SARS patients, patients

Table 5
Possible dosages and schedule of therapeutic agents for MERS-CoV Infection

Medication	Normal dose Crc l> 50ml/min	Impaired renal function Crcl (20-50 ml/min)	ESRD (Hemodialysis) CrCl< 20ml/min
Ribavirin oral	2000 mg loading dose then 1200mg q8h for 4 days, then 600mg po q8h for 4-6 days	2000 mg loading dose then 600 mg po q8h for 4 days, 200 mg po q6h for 4-6 days	2000 mg loading dose then 200mg po q6h for 4 days, then 200mg po q12h
Peg interferon alfa 2b	1.5mcg/kg once per week x 2	Same dose	Same dose
Lopinavir 400 mg/ ritonavir 100 mg oral	Lopinavir 400 mg/ ritonavir 100 mg twice daily for 10 days. May be given in combination with Ribavirin	Same dose	Same dose
convalescent plasma	300- 500 ml of full plasma (3 – 5 ml/kg) With a rate of 2ml/min for one time in day 2 of ICU admission.	Same dose	Same dose

in the plasma group had a shorter hospital stay (58.3% -73.4% versus 15.6%- 19%; $P < 0.001$)[21,22] and lower mortality than the comparator group (0%- 12.5% versus 17% 23.8%).[19,21,22]

Intriguingly, an in vitro study showed that convalescent plasma from SARS patients might contain cross-reactive antibodies against other beta-coronavirus including MERS-CoV.[24] Of 28 sera, 7 (25%) had antibodies anti-MERS-CoV neutralizing antibodies at low titers.[24] Convalescent sera was recommended in a recent study by the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC).[25] Cross- reactive antibodies may be present in convalescent plasma from SARS patients against other beta-coronavirus and may be associated with a better outcome, reduced mortality, and shorter hospital stay.[19–22] There are considerable technical hurdles to overcome before convalescent sera can be widely recommended as a therapeutic agent in the modern era. Currently, there is a need to establish a serology test to diagnose patients with mild disease and thus identify those patients as possible donors of convalescent sera.

We conclude that the use of ribavirin may improve the outcome and reduce mortality as shown in a number of studies. One of the reasons for the failure of ribavirin in some reports may have been the timing for the use of ribavirin, after 6-14 days of symptom,[11,14,16] compared to studies which showed benefits when ribavirin was started within 48 hours of hospitalization or after diagnosis of SARS was established.[8,9,12,13]The major limitation of Ribavarin is its significant toxicity at the doses used to treat patients with SARS. Although the addition of lopinavir/ritonavir to ribavirin appeared to have a better outcome in patients with SARS.[17,18] There are reports that lopinavir/ritonavir is not active in vitro against the MERS-CoV.[25] Other in vitro studies have failed to yield potent therapeutic agents despite a search including DPP4 inhibitors.[26]

Among the limitations of this review are the heterogeneity of the reviewed studies in terms of the wide range of treatment dosages, frequency, and route of administration, duration, and timing of administration. The reported treatment effects should be interpreted with caution due to the lack of randomized, controlled trials.

Also, while we have drawn on the SARS literature, and SARS is a closely related virus, there are clearly differences between SARS and the MERS-CoV and the data might not be able to be directly extrapolated to MERS-CoV infected patients. The use of the discussed agents would require monitoring hematological and biochemical parameters during treatment to detect and prevent adverse effects associated with therapy. Possible dosages of discussed agents especially with unavailability of intravenous ribavarin are listed in Table 5. The table also includes the possible dosage of pegelated interferon-α (PegIFN—α) that is commonly used in the treatment of hepatitis C virus infection. PegIFN-α was 50-100 times more effective *in vitro* for MERS-CoV than SARS-CoV.[25] The long half-life of PegIFN-α and the associated adverse effects calls for extra attention for the use of shorter-acting interferon.[25] The use of interferon therapy with ribavirin is not recommended in patients with hepatitis C virus infection and renal dysfunction (Clcr <50 mL/minute).

With the emergence of MERS-CoV and the lack of high quality clinical evidence to support recommendations for the use of available therapeutic options, there is a clear need for developing protocols to be used in randomized-controlled trials in order to determine the most effective therapies for this novel emerging pathogen.

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