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Case report

Ribavirin and interferon-α2b as primary and preventive treatment for Middle East respiratory syndrome coronavirus: a preliminary report of two cases

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Middle East respiratory syndrome coronavirus (MERS-CoV) is a newly recognized transmissible viral infection with high virulence and case fatality rates for which there is no currently defined primary treatment or prophylaxis. Saudi Arabia has the largest reported number of cases so far. Like severe acute respiratory syndrome (SARS), MERS is caused by a coronavirus. Combination therapy with interferon-α2b and ribavirin has been used successfully as primary treatment and prophylaxis in SARS. Because of similarities between the two coronaviruses, treatment with ribavarin and interferon-α2b has been suggested as a potential therapy for MERS-CoV. Studies in animal models of MERS-CoV have shown the combination of ribavirin and interferon-α2b to be effective both as primary treatment and prophylaxis. In this report, we describe for the first time use of this combination as a primary treatment for a patient with MERS-CoV infection and as prophylaxis for his spouse and discuss its possible role.

Introduction

Coronaviruses are single-stranded, positive-sense RNA viruses. Of the six coronaviruses known to infect humans, two (severe acute respiratory syndrome coronavirus [SARS-CoV] and Middle East respiratory syndrome coronavirus [MERS-CoV]) infections cause severe respiratory syndrome [1]. MERS-CoV is a beta coronavirus distinct from SARS [2]. The number of confirmed cases of severe respiratory disease due to MERS-CoV infection cases has progressively increased since it was first reported in June 2012 [3]. As of October 2013, the World Health Organization (WHO) has reported 178 cases, along with 76 deaths [4].

There are currently no definitive therapies to treat or prevent MERS-CoV-induced respiratory disease [5]. Recently published data, in animal models, shows that MERS-CoV is sensitive to a combination of ribavirin and interferon-α2b [6,7]. This combination reduced viral replication, promoted repair of damaged lung tissue and improved the clinical outcome of MERS-CoV-infected rhesus macaques [6,7]. Moreover, animal studies have also shown that the same combination therapy is effective at reducing disease severity when administered as prophylaxis prior to infection. To date, there are no data to show the potential benefit of this combination in human MERS coinfection.

We report the first two cases, a husband and wife, both health-care professionals, treated with ribavirin and interferon-α2b as primary treatment and prophylaxis, respectively.

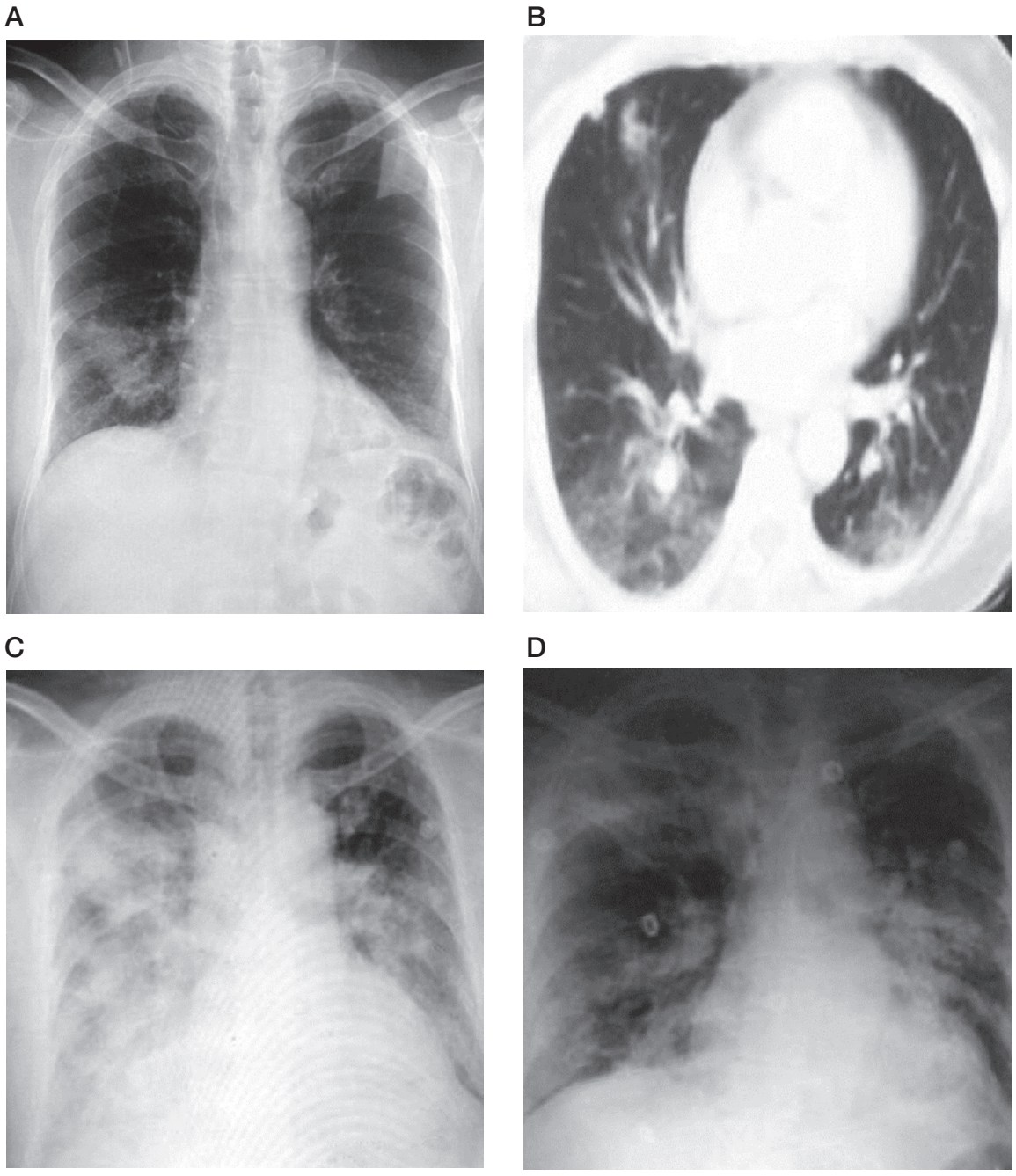
Case report

Patient 1

A 52-year-old male physician was admitted with a history of upper respiratory tract infection and progressive shortness of breath. Besides a temperature of 38.5°C, the rest of the physical exam was unremarkable. The initial laboratory investigation included a haemogram, electrolytes, hepatic and renal profile; all of which were within the normal range.

The initial chest X-ray and chest CT showed small bilateral infiltrates, seen in Figure 1A and 1B. Treatment with broad-spectrum antibiotics (ceftriaxone and azithromycin) was initiated on the first day. Due

Figure 1. Patient 1



(A) Chest X-ray shows infiltrate in right lower lobe. **(B)** CT of chest showing multiple airspace infiltrates. **(C)** Chest X-ray showing bilateral diffuse airspace infiltrates. **(D)** Post-treatment chest X-ray showing significant improvement in bilateral airspace infiltrates.

to increasing case reports of MERS-CoV in the Kingdom of Saudi Arabia, ribavirin and interferon-α2b was started with dosing based on treatment recommendations for SARS, as described in Table 1 [7]. The MERS-CoV infection was confirmed 72 h later by reverse transcriptase (RT)-PCR detection of the consensus viral RNA targets upstream of E gene (UPE) and open reading frame (ORF1b) on a sputum sample. The work up was negative for all other potential pathogens.

The patient developed respiratory failure with worsening X-ray findings on the second and third day (Figure 1C) and required non-invasive ventilation by the third hospital day. He was also started on intravenous methylprednisolone

Table 1. Administration protocol

Agent	Dosing regimen		
	CrCl>50 ml/min	CrCl 20–50 ml/min	CrCl<20 ml/min or on dialysis
Ribavirin	2,000 mg po loading dose, followed by 1,200 mg po every 8 h for 4 days	2,000 mg po loading dose, followed by 600 mg po every 8 h for 4 days then 200 mg po every 6 h for 4–6 days	2,000 mg po loading dose, followed by 200 mg po every 6 h for 4 days then 200 mg po every 12 h for 4–6 days
Pegylated interferon-α2b	180 μg subcutaneously once per week (up to 2 weeks)	180 μg subcutaneously once per week (up to 2 weeks)	180 μg subcutaneously once per week (up to 2 weeks)

All dosing recommendations were adopted from Al Tawfiq *et al.* [12]. CrCl, creatinine clearance; po, per os (oral).

500 mg which was given for 3 days. On the fourth day, oxygenation improved and weaning of non-invasive ventilation was initiated, with an improvement in chest X-ray findings (Figure 1D).

The patient defervesced on the sixth day and exhibited continued clinical and radiological improvement. Non-invasive ventilation was discontinued on the sixth day and he was later discharged from the intensive care unit on 2 l/min supplemental nasal oxygen on the tenth day. Sputum samples obtained up through hospital day 12 remained positive for MERS-CoV RT-PCR, but all subsequent samples were negative. The patient was discharged home on day 18 without supplemental oxygen after complete recovery.

Patient 2

A 42-year-old female physician, the wife of patient 1, was in close-contact with her husband during his illness. After patient 1 was diagnosed as positive for MERS-CoV by sputum RT-PCR, patient 2 began prophylaxis treatment with ribavirin and interferon-α2b at the same doses as used in her husband (Table 1).

Patient 2 was asymptomatic until day 3 of treatment when she developed a low-grade fever to 38°C but was otherwise asymptomatic with a normal physical exam. Haemogram, renal and hepatic function studies were within the normal limits.

At that time the chest X-ray revealed ill-defined infiltrates in the left lung upper lobe (Figure 2A) and cerfuroxime and azithromycin were added to ribavirin and interferon-α2b to broaden coverage to include community-acquired pneumonia. The initial sputum screen failed to show any pathogens, including MERS-CoV. Routine clinical laboratory tests for influenza, parainfluenza, respiratory syncytial virus, adenovirus, rhinovirus, enterovirus, Epstein–Barr virus, cytomegalovirus, human metapneumovirus, urinary *Legionella* antigane and serology for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* were negative.

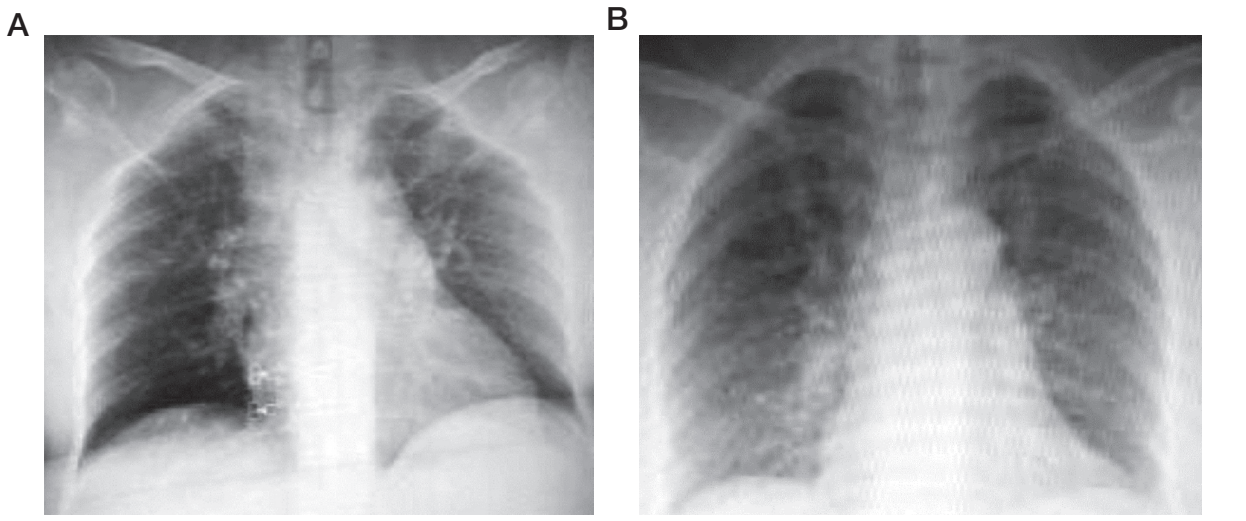
The patient defervesced on the fourth day and follow-up chest X-ray on treatment day 6 showed almost complete resolution of the infiltrates (Figure 2B). Antimicrobials were stopped on day 7. Repeated sputum samples remained negative for MERS-CoV and other pathogens. The patient completed 2 weeks of ribavirin and interferon-α2b therapy and recovered from her mild illness at home. None of the three children in the home developed an acute respiratory illness.

Discussion

MERS-CoV is emerging as a serious endemic illness associated with high mortality. Saudi Arabia is the most affected country, with the majority of reported cases and fatality thus far. Clinical presentation in MERS-CoV is quite variable, ranging from an asymptomatic infection to respiratory and multi-organ failure, with an overall case fatality rate of 60% [8]. The majority of cases are male (65%) with a median age of 51 years [9]. MERS-CoV transmission has been described from person to person, family cluster and in health-care settings, with an estimated median incubation period of 5.2 days [10]. As occurred with SARS, spread to other parts of the world is expected as a consequence of the increase in international travel. There is also the concern that the yearly Hajj (pilgrimage) season, when over 2 million international visitors come to Mecca and Medina, may accelerate the spread [11].

Guery and van der Werf [5] highlighted the need for therapeutic protocols for MERS-CoV. Ribavarin and interferon-α2b were used during the SARS epidemic of 2003. Because of similarities between the two coronaviruses, treatment with ribavarin and interferon-α2b has been suggested as a potential therapy for MERS-CoV. Recently published data, in animal models, shows that MERS-CoV is sensitive to a ribavirin and interferon-α2b combination therapy [6,7]. Both drugs had a virucidal effect at high doses individually, whereas a combination of ribavirin and interferon-α2b had a synergistic virucidal effect at much lower doses, with possible lower toxicity. The animal studies have also shown some prophylactic effect in reducing the severity of the disease in pre-treated animals.

Figure 2. Patient 2



(A) Initial chest X-ray with ground-glass infiltrates left upper lobe. **(B)** Follow-up chest X-ray after treatment showing resolution of ground-glass infiltrates.

To our knowledge, only one study has addressed the use of a combination therapy with ribavirin and interferon-α2b in MERS-CoV in humans. Al-Tawfiq *et al*. [12] reported five patients treated with this combination all had a fatal outcome. However, patients all had severe illness, multiple comorbidities and treatment was introduced late in the course of the disease. Our case report, on the other hand, suggests that patient 1 fared much better than expected and without any detectable side effects of the treatment. Steroids may have helped in his early recovery as has been reported in the SARS epidemic with ribavirin/interferon and steroids [13].

The case study of patient 2 is limited by the lack of definitive diagnosis. Unfortunately, serological studies of MERS-CoV were not available to us. Nonetheless, the timing of her mild respiratory illness with exposure to a patient with documented MERS-CoV infection, suggests that she had a very mild form of MERS-CoV infection. Whether the prophylaxis treatment with interferon-α2b and ribavirin reduced the severity of MERS-CoV infection in this patient is unknown, but based on experience with documented MERS-CoV infection, she had a much milder course than expected.

In conclusion, our case reports describe successful use of interferon-α2b and ribavirin in human MERS-CoV infection. Results are consistent with previous findings in animal models of MERS-CoV. Because of their limitations, case reports such as this are insufficient evidence to make any recommendations regarding therapy. However, with the known high mortality associated with MERS-CoV infection and the potential for rapid international spread of the disease, there is an urgent need to initiate controlled trials to analyse the safety and effectiveness of primary and prophylactic treatment of this infection.

Disclosure statement

The authors declare no competing interests.

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