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The Most Effective Therapeutic Regimen for Patients with Severe Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection

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Abstract

Background: More than two years after its discovery, the Middle East respiratory syndrome coronavirus (MERS-CoV) continues to have a high case-fatality rate. A specific therapy with proven effectiveness for MERS-CoV infections still does not exist.

Method: MERSCoV-positive patients were treated with different suggested treatment options. The virological and clinical progress of these patients in response to the treatment was evaluated.

Results: Both patients had co-morbidities and were critically ill with acute respiratory distress syndrome on mechanical ventilation at the time of diagnosis. Even though low dose ribavirin/ pegylated interferon α combination was started early for the first patient, it was provided late for the second patient. Both patients recovered from their infection.

Conclusion: By evaluating the clinical and virological response of the patients to the different treatment options implicated, it seems that currently the most effective therapy against severe MERS-CoV infection is the low dose ribavirin/ pegylated interferon α combination.

Keywords: MERS-CoV; Interferon; Ribavarin; Intravenous immunoglobulin; ORF 1a

Introduction

The Middle East respiratory syndrome coronavirus (MERS-CoV) was first detected in June 2012 in Saudi Arabia [1]. Since then the virus is predominantly detected in the Arabian Peninsula. Other countries were also involved, but the majority of their affected cases were linked to travel to the Arabian Peninsula or caused by a contact with travelers. In Kuwait, one of the Arabian Peninsula countries, despite active surveillance and vigilance, only three cases have been discovered so far. In this report we describe our experience and findings highlighting the virological response to the different treatment regimens adopted in managing both patients.

Method

Clinical samples were screened for MERS-CoV by real-time RT-PCR targeting the upstream of the E gene (upE). Positive results were confirmed by real-time RT-PCR targeting the open reading frame 1a gene (ORF 1a). Viral RNA was extracted from the samples using MagNA Pure LC Total Nucliec Acid Isolation Kit (Roche). ModularDx Kits Corona SA1 up E-gene and Corona Orf1a (TibMolBiol) were utilized in a LightCycler 2.0 real-time PCR system (Roche) for the investigations. Viral load was determined by extrapolation from the standard curves constructed with different dilutions of positive controls included in each kit [2]. Except for the first sample from both patients 1 and 2 which were bronchoalveolar lavage (BAL) fluid, tracheal aspirations were the only samples processed for viral load estimation. To evaluate the virological response to the therapy, it was intended to perform quantitative virus detection every two days. However, due to the instability of the patients and difficulty in collecting samples the test was done less frequently.

Case Reports

Patient 1

A 47 year old Kuwaiti man, long-term smoker, known to have diabetes, hypertension, and peptic ulcer was admitted to the hospital on November 7, 2013, with one week history of fever, cough, and progressive shortness of breath. Seven days before his admission, the patient had returned to Kuwait after a brief travel to Saudi Arabia where he had a possible contact with camels. Before his admission, he presented twice to the Accidents and Emergencies department where he was treated empirically with oral antibiotics. In the hospital, the patient was started on broad spectrum antibiotics and oseltamivir. Methylprednisolone 60 mg/day orally was also added to the treatment regimen. Chest radiography showed bilateral hilar interstitial infiltrates and consolidation in the right lower lobe (Figure 1a).

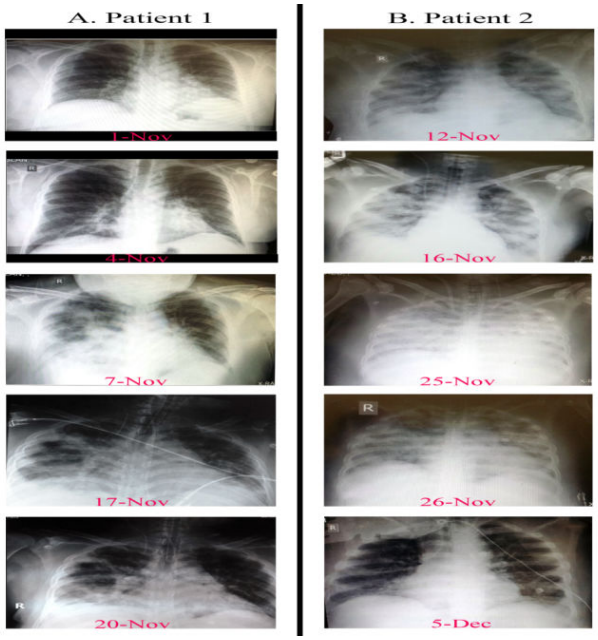

Figure 1a: Panel A shows chest radiography performed for patient 1. The first radiograph was done for the patient in the Accidents and Emergencies department on the day of his arrival from Saudi Arabia. The second radiograph, performed three days later in the Accidents and Emergencies department, shows more apparent right lower lobe involvement. The third radiograph was taken on the day of admission showing marked progression of the infection. Panel B shows chest radiography performed for patient 2. After the addition of ribavirin, marked bilateral reduction of the consolidation could be seen by comparing the radiographs taken on November 25 and November 26. Almost complete clearance of the opacification was achieved by December 5.

Initially the patient was managed with biphasic positive airway pressure (BIPAP). However, his condition continued to deteriorate and, four days later, he developed acute respiratory distress syndrome (ARDS) and was transferred to the intensive care unit where he was intubated for mechanical ventilation. The patient was found to be positive for MERS-CoV by RT-PCR in a BAL fluid on November 11 when the oseltamivir and steroids were discontinued. The patient was started on pegylated interferon α2a (PEG-IFN α2a) 180 μg subcutaneously. Oral ribavirin 400 mg every 12 hours with no loading dose was added by the initial treating physician.

The patient continued to be febrile with temperatures ranging from 38.5-40°C. On November 18, the patient developed acute kidney injury necessitating hemodialysis. On the same day, a second dose of PEG-IFN α2a was given. Two days later, the tracheal aspirate tested negative for MERS-CoV by RT-PCR (Figure 2) and ribavarin was discontinued as a result of gradual drop of the hemoglobin level to 8.9 g/dl (Table 1). The patient was symptomatically managed and steadily continued to improve. The last hemodialysis session he required was on December 2, and he was weaned from the mechanical ventilator on December 9. He was discharged from the hospital on December 23, and started on rehabilitation therapy.

Patient 1:

Date	10/11	11/11	12/11	13/11	17/11	20/11
Urea(2.8-7.1)	10.5	11.9	11.59	9.8	4.9	24.6
Creatinine(70-110)	81	59	58	63	83	81
AST	36	53	45	35	72	81
ALT	53	86	94	81	79	64
WBC	8.9	11.8	14.6	11.9	9.6	9.6
HB	12.1	12.4	12.3	11.8	9.8	8.9
Platlets	154	123	142	144	201	184

Table 1: Blood report of Patient 1.

Patient 2

On November 10, 2013 a 52 year old Kuwaiti man was admitted to the hospital with a seven day history of fever, night sweats, shortness of breath, and dry cough, associated with loss of appetite and diarrhea. He was a heavy smoker obese man with diabetes, hypertension, and ischemic heart disease. Similar to the previous case, this patient had also returned from Saudi Arabia ten days prior to his admission. However, there was no clear history of contact with animals or sick individuals.

On admission, the patient was started on broad spectrum antibiotics and oseltamivir. Chest radiography showed bilateral interstitial infiltrates with lower lobe consolidations and a minimal right sided pleural effusion (Figure 1b). The initial management with BIPAP was not sufficient and, two days later, the patient was transferred to the ICU where he was intubated for mechanical ventilation. The patient was found to be positive for MERS-CoV by RT-PCR in a BAL fluid on November 13. On the next day subcutaneous pegylated interferon-α2b (PEG-INF α2b) 1.5 μg/kg was given. Intravenous corticosteroids (prednisolone 100 mg/day and hydrocortisone 100 mg three times a day) were also added briefly and were discontinued three days later. The patient continued to rapidly deteriorate which demanded the utilization of extracorporeal membrane oxygenation (ECMO) on November 16. The next day, the patient was started on hemodialysis as a result of acute renal failure. Packed red blood cells were also transfused for the first time as a result of progressive anemia.

The patient showed no signs of improvement. His condition continued to worsen becoming anuric and fully dependent on ECMO support for oxygenation. A second dose of PEG-INF α2b was administered on November 21. Intravenous immunoglobulin (IVIG) (400 mg/kg/day for three days) was also added. However, due to the continuous clinical deterioration of the patient, oral ribavirin was added to the treatment on November 24. A loading dose of 800 mg was given followed by 200 mg every 8 hours. Amazingly, significant clinical and virological improvement was noticed. His chest radiography showed marked decrease in the consolidation bilaterally after showing a complete "white out" one day earlier (Figure 1b).

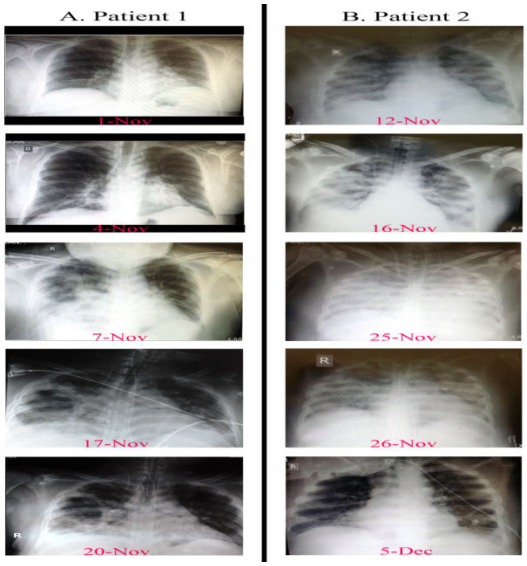

Figure 1b: Panel A shows chest radiography performed for patient 1. The first radiograph was done for the patient in the Accidents and Emergencies department on the day of his arrival from Saudi Arabia. The second radiograph, performed three days later in the Accidents and Emergencies department, shows more apparent right lower lobe involvement. The third radiograph was taken on the day of admission showing marked progression of the infection Panel B shows chest radiography performed for patient 2. After the addition of ribavirin, marked bilateral reduction of the consolidation could be seen by comparing the radiographs taken on November 25 and November 26. Almost complete clearance of the opacification was achieved by December 5

The third PEG-INF α2b was given on November 28. Symptomatic management of the patient included repeated packed red blood cells transfusions and erythropoietin injection to compensate for the hemolytic anemia. On December 3, the patient was weaned from ECMO and MERS-CoV was found to be negative for the first time in endotracheal secretion (Figure 2).

Viral load estimation based on Orf1a quantification is almost always higher than that based on upE quantification. Eventhough, Orf1a and upE became undetectable in Patient 1 at the same time, Orf1a persisted for a longer duration than upE in Patient 2. We should also mention that blood, urine and stool samples were consistently negative for both patients at different stages of the infection. With regards to Patient 3, Orf1a quantification was 4.76×10^4 copies/ml and upE quantification was 4.64×10^4 copies/ml.

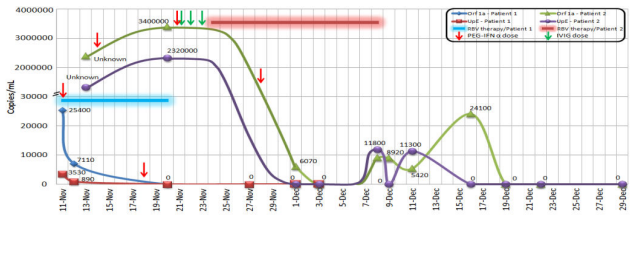

Figure 2: Graph showing the progression of MERS-CoV viral load in samples from patients 1 and 2 in response to antiviral therapy. Except for the first sample from both patients 1 and 2 which were BAL fluid, tracheal aspirations were the only samples processed for viral load estimation. The value beside each marker denotes the viral load. The lines between markers indicate estimated viral loads based on marker values and clinical progress. Quantification of upE and Orf1a was performed on the same sample. Orf1a and upE quantification could not be performed on the first sample of Patient 2 (on November 13).

Patient 2:

Date	23/11	24/11	4/12	6/12	7/12	8/12
Urea(2.8-7.1)	10.6	12.5	21.63	10.24	9.6	10.7
Creatinine(70-110)	161	173	172	132	102	86
AST	65	73	54	56	44	48
ALT	37	33	59	42	34	36
WBC	11.7	14.56	15.7	7.14	6.2	9.68
HB	8.8	7.4	8.1	9	11.4	8.1
Platelets	34	32	104	73	59	82

Table 2: Blood reports of Patient 2.

Ribavirin was discontinued on December 8. Interestingly, on the same day MERS-CoV was detectable again in endotracheal secretion. However, the antiviral treatment was not restarted as the patient continued to show clinical improvement and one week later he was undergoing trials of weaning from the mechanical ventilator. On December 19, MERS-CoV was undetectable again in endotracheal secretion by RT-PCR. Unfortunately, after his recovery from MERS-CoV infection, the patient passed away more than a month later, on February 2, as a result of multiple hospital acquired infections with multidrug resistant organisms (Table 2).

Patient 3

A 60 year old Syrian man, known to have diabetes and hypertension, was admitted to the burn center on February 13 with 12% second degree burns. The patent was having a mild fever of 38°C that was attributed to the burn. Skin grafting was performed on February 19. However, the condition of the patient worsened. His chest infection was more apparent at this stage, and on February 24, he was transferred to the ICU as a result of dyspnea and desaturation where he was intubated for mechanical ventilation. The patient was managed with broad spectrum antibiotics despite negative microbiological and virological investigations. On March 5, the patient was found to be positive for MERS-CoV by RT-PCR in a nasopharyngeal swab sample. Unfortunately, the he died on the same day. Unlike the previous two cases, this patient had no history of recent travel before his admission. He was a driver of a refrigerated truck working in meat transportation. Even though this patient did

not receive antiviral therapy, he is included in this report to demonstrate how difficult it can be to diagnose infected patients.

Highlights: Two MERS-CoV infected patients were successfully treated

- Different treatment options were utilized
- Clinical and virological parameters of both patients were closely monitored
- The most effective treatment option was , PEG-INF α/Ribavirin combination
- The most sensitive virological monitoring/diagnosis test was Orf1a real-time PCR

Discussion

Apart from general supportive care there is still no proven or licensed therapy for the management and treatment of MERC-CoV. However, since MERC-CoV is phylogenetically related to SARS and both cause ARDS [1], treatment options that were used during the SARS outbreak are being considered for MERS-CoV management. This includes the use of interferon monotherapy which has been preferred over the use of interferon and ribavirin combination [3]. This was based mainly on the potential harmful side effects of the combination. In addition, the use of ribavirin alone for the management of MERS-CoV infection was also believed to be associated with an unfavorable safety profile since high doses of the drug were assumed to be needed to approach the required inhibitory concentration *in vivo* [4].

It was intended to treat the first patient with PEG-IFN α2a monotherapy. However, ribavirin 400 mg every 12 hours with no loading dose was added by the initial treating physician. After taking over, the drug was not discontinued by the specialist since the dose was not high and the patient did not have contraindications for the drug. Within one week of therapy, when the condition of the patient was stable enough to allow for the collection of tracheal aspirates, MERS-CoV was undetectable in that sample (Figure 2). At this stage, it was not possible to attribute the rapid virological response of the patient to the PEG-IFN α/ribavirin combination. The patient developed the frequent hemolytic anemia known to be associated with this combination which led to the discontinuation of ribavirin nine days after its initiation. However, his situation was possible to manage with few blood transfusions.

The effect of the PEG-IFN α/ribavirin combination can be more elucidated by examining the response of the second patient whose case was more complicated. This patient developed acute renal failure and progressive anemia early during the course of his MERS-CoV infection complicating the utilization of ribavirin in the therapy. Therefore, PEG-INF α2b and a brief course of intravenous corticosteroids were used as a first line therapy. However, due to his continuous deterioration and lack of clinical and virological response, IVIG was added with the intention to modify the inflammatory response and possibly provide the patient with cross reactive antibodies against MERS-CoV. The effect of the addition of IVIG was negligible and the condition of the patient worsened even further reaching a critical stage. As a result, ribavirin was added as a desperate measure to save the patient despite contraindications. The PEG-IFN α/ribavirin combination resulted in significant clinical, radiological, and virological improvements. The tracheal aspirates became negative for MERS-CoV nine days after the addition of ribavirin (Figure 2). Interestingly, the virus was detectable again in tracheal aspirates five days later despite the continuous administration of ribavirin. It is possible the reason for this reactivation is the fading of the effect of the last dose of PEG-INF α2b which was administered ten days before, resulting in the patient receiving ribavirin monotherapy for three days. Even though this reactivation seemed to be of little clinical significance, it may indicate that monotherapy with lower doses of ribavirin is not sufficient to inhibit the replication of MERS-CoV, therefore, supporting the proposed synergistic effect of PEG-IFN α and ribavirin [4].

The most important adverse reaction of the PEG-IFN α/ribavirin combination experienced in treated patients was the drop in hemoglobin level. Few blood transfusions, in addition to erythropoietin for the second patient, were sufficient to stabilize the hemoglobin level above 9 g/dl. No life threatening side effects were witnessed.

It is interesting that the second patient responded well to the treatment even though ribavirin was added 14 days after his admission. Other published cases treated with a related combination were less successful [5]. One reason for this inconsistency could be the early initiation of PEG-IFN α in our case which may have played an important role in enhancing the response to the combination later. Another reason is our utilization of PEG-IFN α which is possibly more effective than the standard IFN α against MERS-CoV.

Another interesting feature that should also be noticed is that the Orf1a was detectable by RT-PCR for a longer duration and in higher quantity than the upE. This may indicate that testing for the Orf1a is more sensitive than the upE for screening and following up patients (Figure 2).

Although the findings highlighted above may indicate that the of PEG-IFN α/low dose ribavirin combination is the most effective therapy for the treatment of MERS-CoV infected patients, stronger evidence is still needed for the determination of the most effective and safest treatment regimen for this infection.

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References

1. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus ADME, Fouchier RA (2012) Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 367: 1814-1820.
2. Corman V, Eckerle I, Bleicker T, Zaki A, Landt O, et al. (2012) Detection of a novel human coronavirus by real-time reverse-transcription polymerase chain reaction. Euro Surveill 17. pii: 20285.
3. Brown C, Carson G, Chand M, Zambon M (2014) Clinical Decision Making Tool for Treatment of the MERS-CoV v.1.1, 29 July, 2013.
4. Falzarano D, de Wit E, Martellaro C, Callison J, Munster VJ, et al. (2013) Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin. Sci Rep 3: 1686.
5. Al-Tawfiq JA, Momattin H, Dib J, Memish ZA (2014) Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. Int J Infect Dis 20: 42-46.