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Viral Infections (J Tang, Section Editor)

Therapeutic Options for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection: How Close Are We?

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Abstract

Over 1100 cases of MERS-CoV have been reported since it was first identified in June 2012. Clinical presentation ranges from asymptomatic or mild illness to rapidly progressive disease with multi-organ failure and high mortality. Treatment has been largely supportive. A large number of compounds have been shown to have significant in vitro inhibitory activity against MERS-CoV. Until recently, macaques were the only suitable animal models for animal studies, hindering further clinical development of MERS-CoV therapy. However, the recent successful development of MERS-CoV infection model in transduced mice offers opportunities to accelerate clinical development of therapeutic agents for MERS-CoV infection. Currently available evidence supports further clinical investigation of interferon-based treatment regimens for patients with MERS-CoV. Combining interferon with mycophenolate and/or high-dose ribavirin appears especially promising. Monoclonal antibodies against various targets within MERS-CoV Spike protein have yielded encouraging in-vitro results. However, their safety and efficacy require confirmation in animal models and exploratory clinical trials.

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Introduction

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was first identified from a 60-year patient who died in a hospital in Jeddah, Saudi Arabia in June 2012 with severe pneumonia complicated by multi-organ failure [1]. Thereafter, retrospective testing of respiratory and serum samples identified MERS-CoV as the cause of a hospital-based outbreak of undiagnosed respiratory infections in Zarga, Jordan in April 2012 [2, 3]. Up to 16 April 2015, a global total of 1106 cases of MERS-CoV infection has been reported to the World Health Organization (WHO) [4]. The majority of infections have been reported from countries in the Arabian Peninsula and the Middle East, including Saudi Arabia, United Arab Emirates, Qatar, Oman, Kuwait, Yemen, Jordan, Egypt, Lebanon, and Iran [5]. Cases have also been reported from countries outside this region, including the UK [6], Germany [7], France [8], Italy [9], Greece [10], the Netherlands [11], Austria [12], Turkey [13], Tunisia [14], Algeria [15], The Philippines [16], Malaysia [17], and the USA [18]. All such cases involved individuals who were either recently in the Arabian Peninsula or the Middle East, or someone who had recent contact with such individuals.

MERS-CoV infections occur in the community sporadically or in small clusters [19]. However, larger MERS-CoV outbreaks have mostly been associated with nosocomial transmission, mostly resulting in high rates of morbidity and mortality [20–22]. Human-to-human transmission is well documented [19–21, 23, 24]. However, once effective infection control measures are implemented, the virus' potential to cause self-sustained epidemics appears low at present [20, 22, 25, 26].

Dromedary camels have emerged as important hosts of MERS-CoV [27]. MERS-CoV neutralizing antibodies were detected in dromedary camels from Saudi Arabia [28], Oman [29, 30], United Arab Emirates [31–33], Jordan [34], and even Egypt [35], Eastern Africa [36, 37], Nigeria [37], Tunisia [37], and the Canary Islands [29] where primary human MERS-CoV infections have never been reported. Moreover, MERS-CoV genome and viable virus were isolated from dromedary camels from different parts of the Arabian Peninsula [28, 38, 39]. The strongest available evidence of a link between camels and human MERS-CoV infection was the simultaneous isolation of nearly identical MERS-CoV strains from camels and epidemiologically linked human cases in Saudi Arabia [40] and in Qatar [41]. MERS-CoV is more commonly detected in juvenile than older camels, suggesting that younger dromedary camels may have a particularly important role in the virus' epidemiology [42]. Interestingly, recently published results of a large, nationwide sero-survey in Saudi Arabia showed that the prevalence of MERS-CoV antibodies was significantly higher in individuals with frequent contact with animals; 15 times higher in shepherds ($P=0.0004$) and 23 times higher in slaughterhouse workers ($P<0.0001$), compared with the general population [43].

MERS-CoV was also isolated from a single bat in Saudi Arabia [44]. Moreover, a closely related coronavirus was isolated from bats in South Africa [45]. Phylogenetic analysis of the latter suggested that, like many other human coronaviruses, MERS-CoV ancestors might exist in Old World bats [46]. It is therefore possible, although hitherto unconfirmed, that the epidemiology of MERS-CoV involves bats as natural reservoirs and dromedary camels as intermediate or co-hosts [47, 48].

The clinical spectrum of MERS-CoV ranges from a completely asymptomatic illness to rapidly progressive and fatal disease [49–51]. The majority of hospitalized patients have fever, cough, and shortness of breath, with radiological evidence of a lower respiratory tract infection. Gastrointestinal symptoms, headache, and generalized fatigue are also common [7, 22, 52]. Respiratory, renal, and other organ failure are frequent complications of severe MERS-CoV infection, and many patients require admission to an intensive care unit [22, 52, 53]. Although overall mortality is around 38.1 %, mortality is considerable higher in patients with severe MERS-CoV infection [4, 22, 54, 55].

Supportive care has been the mainstay of management for patients with MERS-CoV infection [5, 13, 56]. However, a number of pre-clinical and investigational therapeutic approaches have been described. We herein review potential therapeutic options for patients with MERS-CoV infection.

In vitro studies

In vitro testing of agents already approved for anti-viral or other clinical indications for anti-MERS-CoV activity has the obvious advantages of having established pharmacokinetics properties and safety profiles. Numerous such agents have been tested in cell culture and several have been found to have some inhibitory activity against MERS-CoV (Table 1).

Interferon products have significant in vitro MERS-CoV inhibitory activity. However, interferon beta is most potent in vitro demonstrating in vitro activity that is 16-fold higher than interferon alfa-2b, 41-fold higher than interferon gamma, and 117-fold higher than interferon alfa-2a [57]. Even more, interferon gamma showed no useful in vitro MERS-CoV inhibitory activities in some studies [58]. Of note, MERS-CoV is 50–100 times more sensitive in vitro to interferon alfa than severe acute respiratory syndrome coronavirus (SARS-CoV) [59]. Therefore, the clinical experience gained with interferon therapy during SARS outbreak may not be directly applicable to MERS-CoV [63].

Falzarano et al. assessed in vitro activity of interferon alfa-2b alone or in combination with ribavirin using Vero and LLC-MK2 cell lines [60]. They noted that both compounds demonstrated useful anti-MERS-CoV activity in Vero cells only at concentrations higher than those than can be achieved clinically (Table 1). However, their activity was several folds higher in LLC-MK2 cells [60]. Vero cells are known to be relatively resistant to ribavirin; an observation that might explain the consistently high 50 % inhibitory concentration (IC_{50}) values reported in assays utilizing this cell type [57, 58, 64]. Moreover, when both interferon alfa-2b and ribavirin were applied as a combination, significant synergism was observed with eightfold reduction in IC_{50} for interferon alfa-2b and 16-fold reduction in that of ribavirin (Table 1) [60]. Similar synergism was previously demonstrated for interferon plus ribavirin against SARS-CoV [65, 66].

Mycophenolic acid consistently demonstrated potent in vitro MERS-CoV inhibitory activity (Table 1) [57, 58]. It is thought to exert its antiviral effects through modulation of interferon-stimulated gene expression [67, 68]. Mycophenolic acid is widely used as an immune suppressive agent of recipients of organ transplantation and other clinical indications; further clinical evaluation of its potential role in the treatment of patients with MERS-CoV infection is warranted.

Cyclosporin A appears to function through blocking of interactions between viral proteins and cellular cyclophilin [69]. It has been shown to prevent MERS-CoV cytopathic effects and prevent cell death in cell culture [59]. However, some cells continued to support low-level MERS-CoV replication, raising concerns over the possible emergence of resistance to cyclosporine during clinical treatment.

Other anti-MERS-CoV compounds have been identified through in vitro screening of large libraries. Using a cytopathic effect assay, a library of 348 FDA-

Table 1. Summary of in vitro anti-MERS-CoV activity of selected agents

Agent	In vitro model	Findings	References
Interferon beta	Cell-based ELISA in Vero E6 cells	IC_{50}, 1.37 U/mL, IC_{90} 39 U/mL	Hart et al. [57]
Interferon alfa-2a	Cell-based ELISA in Vero E6 cells	IC_{50} 160.8 U/mL	Hart et al. [57]
Interferon alfa-2b	Cell-based ELISA in Vero E6 cells	IC_{50} 21.4 U/mL	Hart et al.[57]
Interferon gamma	Cell-based ELISA in Vero E6 cells	IC_{50} 56.5 U/mL	Hart et al. [57]
Interferon alfa-2b	CPE in Vero cells	EC_{50} 6709 U/mL, EC_{90} 184,015 U/mL	Chan et al. [58]
Interferon beta-1a	CPE in Vero cells	EC_{50} 480 U/mL, EC_{90} 2473 U/mL	Chan et al. [58]
Interferon beta-1b	CPE in Vero cells	EC_{50} 17.64 U/mL, EC_{90} 93.31 U/mL	Chan et al. [58]
Interferon alfa	CPE in Vero cells	Profound inhibition of MERS-CoV CPE	de Wilde et al. [59]
Interferon alfa-2b	CPE in Vero cells	IC_{50} 58.08 U/mL, IC_{90} 320.11 U/mL	Falzarano et al. [60]
Interferon alfa-2b	CPE in LLC-MK2 cells	IC_{50} 13.26 U/mL, IC_{90} 44.24 U/mL	Falzarano et al. [60]
Ribavirin	Cell-based ELISA in Vero E6 cells	Inhibitory MERS-CoV effect at concentrations ≥250 μM	Hart et al. [57]
Ribavirin	CPE in Vero cells	EC_{50} 9.99 μg/mL, EC_{90} 107 μg/mL	Chan et al. [58]
Ribavirin	CPE in Vero cells	IC_{50} 41.45 μg/mL, IC_{90} 92.15 μg/mL	Falzarano et al. [60]
Ribavirin	CPE in LLC-MK2 cells	IC_{50} 16.33 μg/mL, IC_{90} 21.15 μg/mL	Falzarano et al. [60]
Ribavirin plus interferon alfa-2b	CPE in Vero cells	Ribavirin IC_{50} 12 μg/mL; interferon IC_{50} 62 u/mL	Falzarano et al. [60]
Mycophenolic acid	Cell-based ELISA in Vero E6 cells	IC_{50} 2.87 μM	Hart et al. [57]
Mycophenolic acid	CPE in Vero cells	EC_{50} 0.17 U/mL, EC_{90} 2.61 U/mL	Chan et al. [58]
Cyclosporin A	CPE in Vero and Huh7 cells	Treatment with 9–15 μM Cyclosporin A inhibited MERS-CoV CPE	de Wilde et al. [59]
Lopinavir	CPE in Vero or Huh7 cells	EC_{50} 8.0 μM, CC_{50} 24.4 μM	de Wilde et al. [61]
Loperamide	CPE in Vero or Huh7 cells	EC_{50} 4.8 μM, CC_{50} 15.5 μM	de Wilde et al. [61]
Chloroquine	CPE in Vero or Huh7 cells	EC_{50} 3.0 μM, CC_{50} 58.1 μM	de Wilde et al.[61]
Chloroquine	Cell-based ELISA in Vero E6 cells	EC_{50} 6.275 μM	Dyall et al. [62]
Chlorpromazine	CPE in Vero or Huh7 cells	EC_{50} 4.9 μM, CC_{50} 21.3 μM	de Wilde et al. [61]
Chlorpromazine	Cell-based ELISA in Vero E6 cells	EC_{50} 9.51 μM	Dyall et al. [62]
Trifluprom azine	Cell-based ELISA in Vero E6 cells	EC_{50} 5.76 μM	Dyall et al. [62]
Dasatinib	Cell-based ELISA in Vero E6 cells	EC_{50} 5.47 μM	Dyall et al. [62]
Imatinib	Cell-based ELISA in Vero E6 cells	EC_{50} 17.69 μM	Dyall et al. [62]
Gemcitabine	Cell-based ELISA in Vero E6 cells	EC_{50} 1.22 μM	Dyall et al. [62]
Toremifene	Cell-based ELISA in Vero E6 cells	EC_{50} 12.92 μM	Dyall et al. [62]

CC_{50} 50 % cytotoxic concentration, *EC_{50}* 50 % effective concentration, *CPE* cytopathic effect, *IC_{50}* 50 % inhibitory concentration, *IC_{90}* 90 % inhibitory concentration, *INF* interferon

approved agents was tested for in vitro MERS-CoV activity [61]. Chloroquine, chlorpromazine, loperamide, and lopinavir were found to inhibit MERS-CoV

replication at low concentrations. Lopinavir had previously been shown to inhibit SARS-CoV replication in vitro and was suggested as a possible therapeutic option for MERS-CoV [70, 71]. However, in another large in vitro study, out of 1280 compounds that were screened for in vitro MERS-CoV activity, only mycophenolic acid, ribavirin, interferon alfa-2a, interferon beta-1a, and interferon beta-1b showed anti-MERS-CoV activity, while lopinavir, nelfinavir, and interferon gamma demonstrated suboptimal activity [58].

Dyall et al. used cell-based ELISA assay to screen 290 compounds, all either FDA-approved or in advanced stages development, for anti-MERS-CoV activity [62]. Sixty agents were found to be active against MERS-CoV. These included neurotransmitter inhibitors (e.g., chlorpromazine, trifluprom azine), estrogen receptor antagonists (e.g., tamoxifen), kinase signaling inhibitors (e.g., imatinib, dasatinib), inhibitors of lipid or sterol metabolism (e.g., terconazole, triparanol), protein processing inhibitors (e.g., anisomycin, homoharringtonine), inhibitors of DNA synthesis or repair (e.g., Gemcitabine), and anti-malarial agents (e.g., chloroquine, mefloquine) [62].

Most of the agents described above are readily available for clinical use in their respective licensed indications. Although their optimal use needs confirmation in appropriately conducted clinical trials, they may be used off-label at the discretion of physicians treating patients with MERS-CoV infection.

Pre-clinical, in vitro studies

MERS-CoV carry Spike (S) proteins on their envelope through which they bind to specific receptors on its host cells; dipeptidyl peptidase (DPP4), also known as CD26 [72]. S protein is composed of S1 and S2 subunits (Fig. 1). S protein binds to DPP4 at a receptor-binding domain (RBD) on S1 subunit. S2 subunit mediates membrane fusion and includes in its structure two heptad repeat domains (HR1 and HR2), in addition to a fusion protein (FP), and transmembrane (TM) and cytoplasmic (CD) domains [48, 73, 74].

RBD of MERS-CoV S1 glycoprotein can induce significant neutralizing antibody response [75, 76]. A monoclonal antibody, designated Mersmab1, was produced in mice immunized with recombinant MERS-CoV S1 fused to IgG1 Fc. Mersmab1 blocks MERS-CoV entry and inhibits cytopathic effects in cell culture [77]. Screening large non-immune human antibody libraries for MERS-CoV1 RBD neutralizing activity resulted in the identification of several potent monoclonal antibodies (Fig. 1) [78–80]. For example, three highly potent human monoclonal antibodies, m336, m337, and m338, neutralized pseudo-typed MERS-CoV in cell culture with IC_{50} ranging between 0.005 and 0.017 μg/mL; m336, which is the most potent of the three, had an IC_{90} of 0.039 μg/mL [80].

Inhibition of MERS-CoV through DPP4 is another potential target for anti-MERS-CoV therapeutics [81]. Adenosine deaminase is a natural antagonist for DPP4 and has been shown to prevent MERS-CoV infection in DPP4-transfected cells [82]. Anti-CD26 monoclonal antibodies such as 2F9 and YS110 inhibited binding of MERS-CoV to DPP4 and prevented MERS-CoV infection in Huh-7 cells [83]. However, DPP4 is expressed on the epithelial and endothelial cell of most human organs and is involved in many important functions including

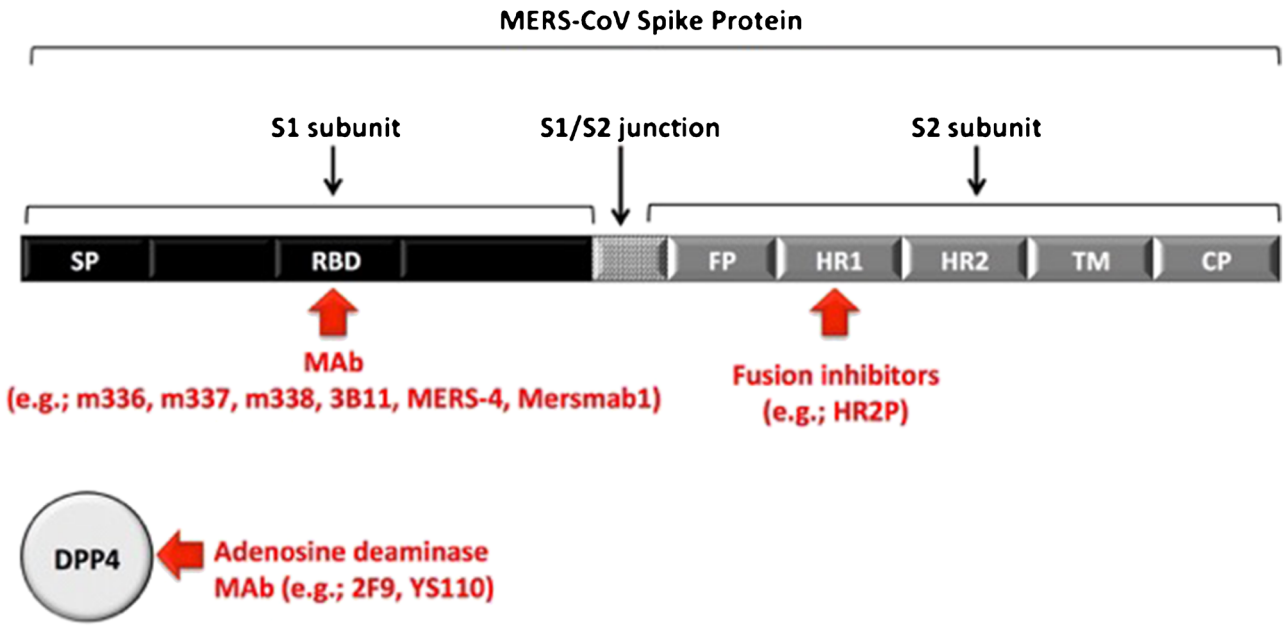

Fig. 1. MERS-CoV Spike protein structure and selected therapeutic targets. CD, cytoplasmic domain; DPP4, dipeptidyl peptidase 4; FP, fusion peptide; HR, heptad repeat; MAb, monocolonal antibodies; RBD, receptor binding domain; SP, signal peptide; S, spike; TM, trans-membrane domain.

glucose metabolism, T-cell activation, chemotaxis modulation, cell adhesion, and apoptosis [84]. Therefore, non-selective DPP4 inhibition in humans may result in pleiotropic effects on the host and trigger unexpected adverse events.

Another entry mechanism for MERS-CoV is through S2-mediated membrane fusion [48, 74, 85]. HR2P, a synthetic peptide, blocks HR1 domain on MERS-CoV S protein and exhibits potent anti-viral effect in vitro (Fig. 1) [85]. The HIV-1 fusion inhibitor Enfuvirtide (T-20), which is licensed for the treatment of patients with HIV infection, is an HR2 peptide [86]. MERS-CoV HR2P analogs are therefore realistic potential options for MERS-CoV therapy that require further ex vivo and in vivo assessment.

These monoclonal antibodies and investigational peptides are promising candidates for further evaluation. Their exceptionally high neutralization activity renders them potential options for prevention or treatment of MERS-CoV infection. Non-immune antibody libraries have thus far been used to identify those potent MERS-CoV human monoclonal antibodies. It would be of great interest to investigate sera from immune individuals for the presence of these antibodies as well as screen them for any others with significant neutralization activity. It should be emphasized that despite their potent in vitro activity, the safety and efficacy of all monoclonal antibodies and peptides will need to be confirmed in animal models followed by human clinical trials [87]. Other potential concern over the clinical application of monoclonal antibodies in MERS-CoV therapy is the emergence of escape mutants and development of resistance [87]. At least in one study, escape mutations from one epitope did not have a major impact on neutralization with antibodies directed against other epitopes [79]. It may there be preferable that MERS-CoV monoclonal antibodies are used in combinations [87].

Animal studies

One of the major earlier challenges in any emerging infectious disease is the development of successful animal models to facilitate experimental investigations to understand the pathogenesis and identify potential therapeutic targets and interventions. DPP4 of wild-type mice does not support MERS-CoV target binding, and hence, no viral replication in lung tissue or infection was evident in experimentally exposed mice [88, 89]. Similarly, MERS-CoV failed to replicate in inoculated small animals such as ferrets or Syrian hamsters [82, 90, 91]. However, following intra-tracheal, ocular, oral, or intra-nasal inoculation with infectious doses of the MERS-CoV, rhesus macaques developed clinical signs of lower respiratory tract infection in addition to compatible histological changes, evidence of virus replication in lung tissue, gene expression, production of neutralizing antibodies, and cytokine and chemokine production [92–94].

Following on from their ex vivo demonstration of antiviral effect of interferon alfa-2b and ribavirin against MERS-CoV [60], Falzarano et al. used macaques to study the clinical efficacy of the combination in experimental MERS-CoV infection [95]. Two sets of three rhesus macaques were infected with MERS-CoV. One set of macaques was commenced 8 h after infection on subcutaneous interferon alfa-2b 5 million units per kg every 16 h with intramuscular ribavirin 10 mg per kg every 8 h. All animals were put down after 72 h of infection. Unlike treated animals, untreated macaques showed signs of respiratory distress, had decreased oxygen saturation, and developed interstitial infiltrates in their chest radiographs. Necropsy showed that lungs of untreated macaques were firm and edematous with multi-focal consolidation whereas treated animals had normal-looking lungs. Mean viral load in lung tissue from treated animals was significantly lower than untreated animals ($P=0.04$). Moreover, treated animals showed reduced systemic and local production of pro-inflammatory cytokines indicating a moderated host response to infection. These findings provide strong support for the potential role of early interferon plus ribavirin therapy in MERS-CoV infected humans. However, administration of therapy as early as 8 h of human infection is probably not feasible in most clinical settings.

One remarkable recent development has been the successful development of an experimental MERS-CoV infection model using mice transduced with recombinant, non-replicating adenovirus expressing hDPP4 receptors [96]. The investigators demonstrated that adenovirus-hDPP4 transduced C57BL/6 and BALB/c mice infected with MERS-CoV failed to gain weight and had viral replication in their lung tissues with pathological evidence of interstitial pneumonia. Furthermore, it was shown that hDPP4-transduced mice without RIG-I-like receptors (RLRs) and Toll-like receptors (TLRs), both required for interferon induction in coronavirus infections, had a more severe MERS-CoV infection and delayed viral clearance. These findings suggest that TLR-dependent and IFN signaling pathways are required for MERS-CoV control. To further investigate the role of interferon in MERS-CoV, Zhao et al. treated adenovirus hDPP4-transduced mice with polyinosinic-polycytidylic acid (poly I:C), an immunostimulant TLR3 agonist, interferon beta or interferon gamma before inoculation with MERS-CoV. Poly I:C and interferon beta therapy resulted in accelerated viral clearance without increased inflammatory cell infiltration [96]. This small

animal model, which is reproducible within 2–3 weeks, offers great potential to accelerate further experimental work to elucidate the detailed host responses involved in MERS-CoV infection and to investigate potential therapeutic interventions, including those described above.

Clinical experience

Clinical data on MERS-CoV therapy remains limited to case reports, case series, and retrospective cohort studies (Table 2). Supported by reports describing the effectiveness of the combination of interferon and ribavirin in vitro and in macaques, this combination has been most widely used. The earliest clinical report emerged from the Eastern Province, Saudi Arabia. Five patients with severe MERS-CoV infection were started on high-dose ribavirin plus interferon alfa-2b after a median of 19 days from hospitalization. All patients were critically ill and had significant co-morbidities. None of the patients survived [97]. The largest study to date included 44 patients with severe MERS-CoV infection requiring respiratory support [53]. Twenty patients who received interferon alfa-2a plus high-dose ribavirin after a median of 3 days from diagnosis were compared with an historic matched cohort of 24 patients. Combination therapy was associated with significantly improved survival at 14-days from diagnosis (70 vs 29 %; P=0.004). There was a strong trend towards improved survival in the combination group at 28-days, but the difference was not statistically significant (30 % vs 20 %, P=0.054) [53].

Similarly, in a recent report from a single center in Jeddah, Saudi Arabia, overall in-hospital mortality was 69 % of 24 patients with severe MERS-CoV infection despite receiving ribavirin plus either interferon alfa-2a or interferon beta-1a within a median of 1 day from diagnosis [98]. Mortality was not significantly different in 13 patients who received interferon alfa (85 %) compared with 11 patients who received interferon beta therapy (64 %, P=0.24) [98]. The sample size in both studies was probably inadequate to demonstrate improved long-term survival, especially that most MERS-CoV patients have significant co-morbidities and that the course of MERS-CoV infection is frequently complicated by hospital-acquired infections that are likely to contribute to the patients' poor outcome [20, 22, 52, 54, 55]. Furthermore, treatment in both studies was started when patients were already ill and requiring respiratory support, in contrast to the macaques study where treatment was commenced within 8 h of experimental infection [95]. Interestingly, initiation of treatment in patients with mild symptoms and radiological evidence of pneumonia was associated with full recovery [99, 100]. Whether initiation of combination therapy earlier in the course of MERS-CoV illness is beneficial is a question that should be addressed in appropriately designed and powered clinical trials.

A case report from Greece described one patient with MERS-CoV infection who died despite triple therapy with interferon alfa-2a, ribavirin, and lopinavir. The patient had multi-organ failure and was later diagnosed with colon cancer. MERS-CoV was not detectable in his respiratory tract for several days before his death [101]. Neither of the two reported patients who had been on cyclosporin prior to MERS-CoV infection for other indications survived [8, 102]. One renal transplant recipient, who was on mycophenolate and prednisolone, survived

Table 2. Clinical experience with therapeutic interventions for patients with MERS-CoV infection

Reference	Patient(s)	Intervention	Outcome
Al-Tawfiq et al. [97]	5 critically ill patients; all with chronic kidney disease, median age 62 years, 3 males.	RBV 2000-mg loading followed by 400–800 mg q12h plus INF alfa-2b 100–144 µg per week. Median time from hospitaliza tion to start of therapy was 19 days (range 10–22).	1 patient developed hemolytic anemia on therapy, and 2 developed high lipase. All patients died within an average of 40 days after admission.
Omrani et al. [53]	44 patients with severe MERS-CoV infection requiring invasive or non-invasive ventilation. Mean (±SD) age was 65.5 (±18.2) years and APACHE II 27 (10.3).	20 patients (treatment group) received RBV 2000-mg loading dose followed by 1200 mg q8h plus peg-INF alfa-2a 180 µg per week within a median of 3 days (range 0–8) from diagnosis. 24 matched historical controls (comparator group) received supportive care only.	Survival in the treatment group and the comparator group was 70 % versus 29 % at 14 days (p=0.004), and 30 % versus 17 % at 28 days (p=0.054), respectivley. The treatment group had significantly more hemoglobin reduction than the comparator group (p=0.002).
Shalhoub et al. [98]	24 patients with MERS-CoV pneu monia, median age 60 years, 56 % males.	RBV 2000-mg loading followed by 600 mg q8h plus either IFN alfa-2a 180 µg per week (n= 13) or IFN beta-1a 44 mg thrice per week (n=11). Treatment was started within a median of 1 day of MERS-CoV diagnosis.	Overall mortality rate was 69 % (22/32). Mortality in patients who received IFN alfa-2a was 85 % (11/13) versus 64 % (7/11) in those who received IFN beta-1a (p=0.24). Age above 50 years and diabetes mellitus were independent risk factors for mortality.
Khalid et al. [99, 100]	6 patients; all with radiological evidence of pneumonia. 3 with severe infection and multi-organ failure requiring MV and CRRT; 1 requiring non-invasive ventilation; 2 with mild/asymptomatic disease.	RBV 2000-mg loading dose followed by 1200 mg q8h plus peg-INF alfa-2b 180 µg per week. Mean time to start of therapy was 14.7 days in 3 pa tients with severe MERS-CoV disease. One patient with moderately severe disease was started on treatment on day of admission to hospital.	All 3 patients with severe disease and multi-organ failure died. All remaining 3 patients sur vived.
Spanakis et al. [101]	69-year old man with bilateral pneumonia, ARDS and respiratory failure requiring MV. AKI on CRRT. Later diagnosed with adenocarcinoma of the colon.	Lopinavir 400 mg/ritonavir 100 mg q12h, peg-INF alfa-2a 180 µg per week and RBV 2000 mg loading followed by 1200 mg q8h. All started on day 13 from onset of illness, day 3 from diagnosis of MERS-CoV infection.	Viremia resolved within 2 days of combination therapy. RBV discontinued after 7 days due to hyperbilirubinemia. Patient died of septic shock 13 days after stopping therapy; 2 post-therapy respiratory samples were negative by RT-PCR for MERS-CoV.
Al-Ghamdi et al. [102]	2 renal transplant patients. Frist is a 44-years old man who pre sented 10-years post-	First patient was on long-term cyclosporine, azathioprine, and prednisone. He was started on	Patient 1 died 7 days after diagnosis. Patient 2 was

Table 2. (Continued)

Reference	Patient(s)	Intervention	Outcome
	transplant with severe, bilateral pneumonia complicated by re spiratory failure, and AKI. He required MV and CRRT. Second patient is a 30-year old man who presented 6 weeks post-transplant with no-pneumonic MERS-CoV infection.	peg-INF alfa-2a 180 µg per week plus RBV 400-mg loading followed by 200 mg q12h on day 8 from admission; 11 days from onset of symptoms. Second patient was on mycophenolate and prednisone. No additional anti-viral therapy was prescribed.	discharged home after 9 days of hospitalization.
Shalhoub et al. [103]	51-year old man with recently diagnosed HIV infection (CD4 count 58 cells/mm^3). Bilateral infiltrates. CMV colitis was di agnosed and treated in the same admission.	Starting day 1 from diagnosis, RBV 2000-mg loading followed by 600 mg q12h plus peg-INF alfa-2a 180 µg per week (9 days), switched to interfer on beta-1a 44 µg thrice weekly (17 days). Also anti-HIV thera py with TDF/FTC and ATV/r and anti-CMV therapy with ganci clovir followed by valganciclovir (21 days).	Depression presumed at least partly secondary to interferon therapy. Discharged home after 39 days of hospitalization. Prolonged viral shedding in respiratory secretions, extended beyond RBV/INF therapy.
Al-Hameed et al. [54]	8 critically ill patients; all in ICU, 7 on MV. Median age 56.5 years, 75 % males, median day 1 in ICU APACHE II score 13 (range 5–30). 6 developed secondary bacterial infections.	All received INF alfa-2a plus RBV (dosing regimen, duration and time to start of therapy not provided).	Non-infectious complications included congestive heart failure (2), acute myocardial infarction (2), pulmonary em-bolism (1), and intra-cranial hemorrhage (1). Final outcome, 5 died, 1 brain-dead and 2 recovered.

AKI acute kidney injury, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *ARDS* acute respiratory distress syndrome, *ATV/r* atazanavir/ritonavir, *CRRT* continuous renal replacement therapy, *FTC* emtricitabine, *ICU* intensive care unit, *INF* interferon, *MV* mechanical ventilation, *peg-INF* pegylated interferon, *RT-PCR* real-time polymerase chain reaction, *RBV* ribavirin, *SD* standard deviation, *TDF* tenofovir dipivoxil fumerate

MERS-CoV infection. However, he did not require any ventilator support and did not receive any anti-viral therapy [102].

There are no published reports of therapeutic use of mycophenolate, cyclosporin, chloroquine, or other agents that have been shown to have anti-MERS-CoV activity in vitro (Table 1).

Conclusion

The recent availability of MERS-CoV infection model in transduced mice provides a much needed opportunity to accelerate clinical development of various compounds with potent in vitro MERS-CoV inhibitory activity. Evidence available so far supports further clinical investigation of interferon beta-, and to a lesser extent interferon alfa-, based treatment regimens for patients with MERS-CoV. Combining interferon with mycophenolate and/or high dose ribavirin

appears especially promising. The role of monoclonal antibody-based MERS-CoV therapy warrants additional investigation in animal models or small exploratory clinical trials. Establishing their safety will be as important as their clinical efficacy.

Compliance with ethics guidelines

Conflict of Interest
Ali Omrani and Ziad Memish declare that they have no competing interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by the author.

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