

A review of treatment modalities for Middle East Respiratory Syndrome

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The Middle East Respiratory Syndrome coronavirus (MERS-CoV) has been a focus of international attention since its identification in 2012. Epidemiologically it is characterized by sporadic community cases, which are amplified by hospital-based outbreaks. Healthcare facilities in 27 countries from most continents have experienced imported cases, with the most significant outbreak involving 186 cases in Korea. The mortality internationally is 36% and guidance for clinical management has yet to be developed. Most facilities and healthcare providers outside of the Middle East receiving patients have no or little experience in the clinical management of MERS. When a case does occur there is likely little time for a critical appraisal of the literature and putative pharmacological options. We identified published literature on the management of both MERS-CoV and the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) through searches of PubMed and WHO and the US CDC websites up to 30 April 2016. A total of 101 publications were retrieved for critical appraisal. Most published literature on therapeutics for MERS are *in vitro* experiments, animal studies and case reports. Current treatment options for MERS can be categorized as: immunotherapy with virus-specific antibodies in convalescent plasma; polyclonal and monoclonal antibodies produced *in vitro* or in genetically modified animals; and antiviral agents. The use of any therapeutics in MERS-CoV remains investigational. The therapeutic agents with potential benefits and warranting further investigation include convalescent plasma, interferon- β /ribavirin combination therapy and lopinavir. Corticosteroids, ribavirin monotherapy and mycophenolic acid likely have toxicities that exceed potential benefits.

Introduction

Middle East Respiratory Syndrome coronavirus (MERS-CoV) was first isolated from a patient in the Kingdom of Saudi Arabia in June 2012. Most of the approximately 1700 incident cases to date have been managed in the Middle East. However, this disease has been exported to 27 countries in North America, Asia, Europe and Africa. The majority of these were solitary cases that did not cause secondary spread. In June 2015, Korea experienced the largest outbreak outside of Saudi Arabia with an extended chain of transmission involving multiple generations of cases, including 186 patients and 36 deaths (20%).¹ This demonstrated the potential of MERS-CoV in widespread human-to-human transmission, leading to disruption of health and socio-economic systems.

Anti-coronavirus therapy is challenging to develop. Coronaviruses are biologically diverse and rapidly mutating. Hence, effective agents for one strain, especially those that target replicative mechanisms, may be useless in another strain. Animal studies are logistically and technically difficult as the number of animal models available is limited and only found in designated biosafety level 3 laboratories.² These challenges result in what we identify as a lack of novel and effective treatment modalities and the paucity of clinical trials. Most of the current treatment options for MERS are extrapolated from the 2003 outbreak of Severe Acute Respiratory Syndrome

coronavirus (SARS-CoV) and the 2009 H1N1 influenza outbreak. A heterogeneous range of treatments is used in MERS patients. For example, in a recent audit³ involving 51 patients in Saudi Arabia, 42 (82.4%) received broad-spectrum antibiotics; 5 (9.8%) received hydrocortisone; and 31 (61%) received antiviral treatments. The antiviral treatments included: interferon- β in 23 (45.1%), interferon- α in 8 (15.7%), and mycophenolate mofetil in 8 (15.7%).

There are fundamental differences between SARS-CoV and MERS-CoV that put in question the basis of applying the evidence from treatment of the former to the latter. Although MERS-CoV is phylogenetically related to the SARS-CoV, there are differences in their biological make-up, pathogenesis and clinical manifestations. In contrast to SARS-CoV, which binds to angiotensin-converting enzyme 2 (ACE-2) receptors, MERS-CoV binds to the receptor dipeptidyl peptidase 4 (DDP4/CD26).^{4,5} MERS-CoV *in vivo* targets a wide variety of cells, including type II alveolar cells, non-ciliated epithelial cells (Clara cells) and endothelial cells, but not ACE-2-expressing ciliated epithelial cells infected by SARS-CoV.⁶ MERS-CoV, unlike SARS-CoV, can also infect and replicate in human monocyte-derived macrophages.⁷ This increases the expression of major histocompatibility complex class I and co-stimulatory molecules leading to a more exaggerated activation of the immune response, including the expression of interleukin-12, interferon- γ and chemokines. These differences in receptor usage and susceptibility to type I and type III

interferon may account for the differences in disease patterns, organ tropism and virus shedding.^{6,8–10}

Current treatment options for MERS can be categorized into immunotherapy with virus-specific antibodies in convalescent plasma, polyclonal and monoclonal antibodies produced *in vitro* and in genetically modified animals, and antiviral agents. Attempts have also been made at repurposing approved pharmaceutical drugs for MERS-CoV treatment. Multiple compounds, including oestrogen receptor and dopamine receptor antagonists, have displayed activity against both MERS-CoV^{11–13} and SARS-CoV¹⁴ in Vero and Huh7 cell models. Considerable data are available, but well-designed clinical trials have yet to be completed because of low case numbers in any one site and the known difficulties of doing trials in outbreak settings.

Search strategy and selection criteria

References to the publications for this review were identified through searches of PubMed, WHO and the US CDC websites up to 30 April 2016. The search terms used were combinations of ‘treatment’, ‘Middle East respiratory syndrome’, ‘coronavirus respiratory illness’ and ‘Middle East respiratory syndrome coronavirus’. In addition, the reference lists of these articles were also considered. The types of studies included *in vitro*, *in vivo* and clinical studies. As most treatment options for MERS-CoV are extrapolated from SARS-CoV, relevant articles on the treatment of these two coronaviruses were reviewed. The full text of each identified study was retrieved. Articles published in foreign languages were all in Chinese, of which one of the authors is a native speaker.

In total, 101 articles were critically assessed (55 MERS-CoV and 56 SARS-CoV). The featured therapeutics included convalescent plasma, immunoglobulin, monoclonal antibodies, ribavirin, protease inhibitors, interferon, corticosteroids, nitazoxanide, and immunomodulatory agents including cyclosporin, chloroquine and mycophenolic acid and fusion inhibitors.

Convalescent plasma and immunoglobulins

Convalescent plasma has been used clinically since 1916 to treat infectious diseases.^{15,16} Convalescent serum was used during the recent SARS and Ebola outbreaks.^{17,18} Any trials undertaken were inadequate in terms of defining the safety and efficacy of this treatment in these diseases. The WHO deemed convalescent plasma as the most promising near-term therapy for MERS in the WHO—International Severe Acute Respiratory and Emerging Infection Consortium MERS-CoV Outbreak Readiness Workshop 2013.¹⁹ However, due to the lack of clinical trials, a WHO position paper published in March 2014 stated that the clinical use of convalescent plasma should be regarded as investigational.²⁰

In vitro and animal studies

In MERS-CoV, prophylactic and therapeutic treatment with high-titre MERS immune camel serum was able to diminish weight loss, reduce lung histological changes and accelerate virus clearance in MERS-CoV EMC/2012-infected mice.²¹

Convalescent plasma from SARS patients was shown via indirect immunofluorescence tests to contain cross-reactive antibodies against other β -coronaviruses including MERS-CoV.²²

However, neutralizing cross-reactivity between SARS-CoV and MERS-CoV has not been demonstrated. These cross-reacting sera are therefore unlikely to be useful therapeutically—an important consideration should MERS affect a country with SARS survivors, such as China, Canada and Singapore.

Novel MERS-CoV-specific poly- and monoclonal antibodies (mAbs)^{23–38} are being developed rapidly. They are produced from immunized animals,^{27–30} antibody human phage libraries^{31–36} and memory B cells of recovered patients.^{37,38} Transchromosomal cattle have successfully generated purified human IgG,²⁷ which rapidly decreased viral lung titres in Ad5-hDPP4 receptor-transduced mice. Monoclonal antibodies targeting the MERS-CoV spike (S) glycoprotein have shown strong neutralizing effects in both *in vitro* and in animal studies. S protein is a surface structural protein critical for virus entry into host cells. In mouse models, transnasal mAb was effective in both prophylactic and post-exposure settings in viral clearance.²⁸ Similarly in rhesus models, mAb administration resulted in reduced lung pathology by computed-tomography evaluation.³⁶ However, the caveat in using mAbs is the potential for viral escape and resistance emergence. Their safety profile and *in vivo* effects need to be further explored.

Clinical data

There are two case reports of using intravenous immunoglobulin (IVIG) to treat MERS.^{39,40} One patient from Saudi Arabia was given IVIG together with high-dose corticosteroids for thrombocytopenia.³⁹ The other was a MERS case imported to the USA. IVIG was given on day 14 of illness.⁴⁰ The patient recovered but the IVIG was unlikely to have been effective due to the expected absence of MERS-CoV antibodies in the USA.

A research protocol for collecting and testing convalescent plasma from recovered MERS patients has been formulated and shared in Saudi Arabia,⁴¹ initiating a feasibility and safety study in May 2014.⁴² This protocol has promoted the clinical characterization of MERS patients, and the screening of recovered and exposed individuals. Its completion is expected in June 2017. However, the study has been hampered by logistical challenges, local technical capacity and donor supply.⁴³ A recent communication from the principal investigator of the study revealed that antibody titres in convalescent plasma are too low to produce a therapeutic effect.³⁸

There were no randomized controlled studies (RCTs) on the utility of convalescent plasma during the SARS outbreaks. One retrospective and four prospective studies on SARS-affected patients undertaken in China, Hong Kong and Taiwan demonstrated earlier discharge, rapid decrease in viraemia and survival benefits.^{18,44–47} Promising outcomes were also observed when delayed administration (median=day 11) of pentaglobin, an IgM-enriched immunoglobulin preparation, led to improved clinical parameters and radiological appearance in 12 severe SARS patients who continued to deteriorate despite corticosteroid and ribavirin therapy.⁴⁸ Similarly, during the subsequent 2009 H1N1 outbreak, a prospective cohort study with 93 intensive care patients showed that the use of convalescent plasma was able to reduce respiratory tract viral load, serum cytokine response and mortality.⁴⁹ This positive effect on H1N1 patients was further confirmed by a multicentre RCT using hyperimmune IVIG in intensive care patients.⁵⁰ Its early administration within 5 days of symptom onset was

associated with a lower viral load and reduced mortality. A systematic review and meta-analysis by the University of Nottingham, which included 32 studies of SARS-CoV infection and severe influenza, concluded that there was a statistically significant reduction in mortality when convalescent plasma was administered early, compared with placebo or no therapy.⁵¹ However, the studies were deemed to be low quality and heterogeneous. They lacked control groups and the effects of convalescent plasma or IVIG could not be discerned from the effects of patient comorbidities, stage of illness or other treatments.

A possible theoretical drawback of convalescent plasma is immunopotentiality of infection by passive immunization. This effect is specific to a limited number of viruses including coronaviruses.²⁰ Severe hepatitis was reported in immunized ferrets, and was thought to be mediated by antibody enhancement of SARS-CoV infection in the liver.⁵² However, this was not reproduced in a monkey model.⁵³ In this model, SARS-CoV S protein-specific IgG levels in monkey lung tissue were found to be increasing after re-challenge with SARS-CoV, but there was no enhancement in viral replication. Immunopotentiality from the clinical use of convalescent plasma or other immune globulin-related products in the treatment of a coronavirus has not been reported.

Plasma products vary regionally depending on disease epidemiology and may not contain therapeutic levels of antibodies. Public Health England's evaluation on UK IVIG showed that it has no MERS-CoV neutralizing activity.⁵⁴ In Saudi Arabia, seropositivity of anti-MERS-CoV was found to be 0%–3.3% amongst healthy volunteers, varying by province, age and exposure to camels from 2010 to 2013.^{55–57}

Interferon

Coronaviruses have been shown to suppress interferon (IFN) response in hosts. A subdued IFN response diminishes antigen presentation and reduces antiviral adaptive Th-1 immune response.^{58,59} Therefore, recombinant IFNs or IFN inducers, especially types I and II, have been identified as a treatment modality for MERS for their ability to augment host response.

In vitro and animal studies

Type I (α , β), type II (γ) and type III (λ) IFNs exhibit activity against SARS-CoV.^{60–66} Of these, IFN- β is the most potent when compared with IFN- α and γ .^{64–66} MERS-CoV is 50–100 times more sensitive to IFN- α than SARS-CoV in Vero cells.⁶⁷ As viruses causing lysis of their target cells are most effectively inhibited by IFNs in uninfected cells, IFNs have their highest utility in prophylaxis or early post-exposure.⁶⁸

IFNs display synergistic characteristics when used in combination in *in vitro* studies. When administered together, IFN- β and IFN- γ inhibited SARS-CoV plaque formation by 30-fold and replication by 3000-fold.^{61,69} The combination of IFN- α 2b and ribavirin was effective in reducing MERS-CoV replication in Vero and LLC-MK2 cells.⁷⁰ When combined, there was an 8- and 16-fold decrease in the dose of IFN- α 2b and ribavirin required, respectively. The biological plausibility of the combination was studied via microarray, which showed that ribavirin and IFN- α targeted MERS-CoV genes involved in pathogen recognition, cytokine release and immune responses.⁷¹ The combination was found to be effective in rhesus macaques⁷² and common marmoset⁷³

models when IFN with ribavirin and/or lopinavir was administered. Treatment led to reduced virus replication, moderated host response and improved clinical outcome.

Clinical data

IFN alfacon-1 and corticosteroids were studied in an open-label, uncontrolled study in 22 patients diagnosed as having probable SARS.⁷⁴ The interferon alfacon-1 and corticosteroids arm had better oxygen saturation, more rapid resolution of radiographic lung abnormalities, and lower levels of creatine kinase compared with the corticosteroid arm. However, there was no standard regimen used and adverse events were not well documented.

In MERS-CoV, the role of IFN- α was highlighted in a study that compared the early immune response in two patients.⁷⁵ The first patient, who succumbed rapidly, was found to have significantly lower IFN- α secretion in serum and bronchoscopy lavage samples than the other patient, who survived the infection. The use of IFN- α 2a and ribavirin was described in four case reports^{76–79} and five retrospective cohort studies.^{80–84} These studies involved mainly critically ill patients requiring mechanical ventilation. The mortality in the five retrospective studies ranged from 50%⁸⁰ to 100%,⁸³ higher than the recognized 36% mortality associated with MERS internationally.⁸⁵ The study methods are heterogeneous and the times at which IFN and ribavirin combination treatment was administered are inconsistently described. One of these studies investigated the impact of earlier administration of IFN and ribavirin.⁸² This study involved 44 mechanically ventilated patients. Twenty-two were given IFN- α 2a and ribavirin and the median time to therapy administration was 3 days. Compared with those who did not receive IFN- α 2a and ribavirin, the treatment group had an improvement in survival at 14 days (mortality in treatment group 30% versus comparator group 70%, $P=0.004$) but not at 28 days (mortality treatment group 70% versus comparator group 83%, $P=0.054$). Another retrospective study showed that there was no significant difference in outcomes between patients who were given combinations of ribavirin with IFN- α 2a or IFN- β 1a.⁸² The mortality in patients who received IFN- α 2a was 85% (11/13) compared with 64% (7/11) in those who received IFN- β 1a ($P=0.24$).

The effect of IFN- β and mycophenolic acid combination therapy was studied in a recent retrospective observational study in Saudi Arabia involving 51 patients.³ Although the univariate analysis demonstrated improved survival in patients treated with this combination, the multivariate analysis, which considered the severity of illness, showed no association between the treatments and survival.

IFNs are well-established agents and routinely available. They are used in viral hepatitis, malignancies such as leukaemia and renal cell carcinoma, and multiple sclerosis. Shorter-acting preparations should be preferred rather than pegylated-IFNs to achieve fast onset of action as their utility has been suggested as being better in early infection. Inhaled IFN- β remains under investigation in Phase 2 trials for patients with asthma.⁸⁶

Protease inhibitors

Protease inhibitors are well-established antivirals, with a favourable toxicity profile, used in the treatment of HIV. Protease inhibitors prevent viral replication by binding to enzymes responsible for

proteolytic cleavage. Lopinavir is one of the HIV protease inhibitors that has been repurposed for SARS and MERS treatment. It was previously shown to block the SARS-CoV main protease, M^{pro}.⁸⁷

In vitro and animal studies

Lopinavir was found to be inhibitory against MERS-CoV, *in vitro* in Vero E6 and in Huh7 cells, at a mean 50% effective concentration (EC₅₀) of 8.0 μM in a screen of 348 FDA-approved drugs for anti-MERS-CoV activity.¹¹ This lopinavir plasma concentration is similar to that observed in patients with HIV.⁸⁸ Atazanavir and ritonavir were found to be inactive in the same screen.¹¹ In a common marmoset model, lopinavir/ritonavir was as effective as IFN-β1b in bringing about improved clinical, radiological and pathological findings in lung tissues, and lower mean viral loads in lung and kidney tissues when compared with untreated animals.⁷³

Clinical data

Observational studies on patients affected by SARS suggested a reduction in mortality and less progression to acute respiratory distress syndrome (ARDS) when lopinavir/ritonavir was combined with ribavirin.^{89,90} Patients who received ribavirin, lopinavir/ritonavir and corticosteroids had lower 21 day ARDS and mortality than those who received ribavirin and corticosteroids.^{89,90} However, all studies were determined by a systematic review to be inconclusive due to selection and treatment biases.⁹¹ Two case reports from Greece⁷⁶ and Korea⁷⁸ showed positive outcomes with lopinavir/ritonavir, type 1 IFN and ribavirin combination therapy. The Greek patient cleared viraemia 2 days after initiation of triple therapy administered on day 13 of illness.

Ribavirin

In vitro and animal studies

Ribavirin has a broad spectrum of activity against viral infections.^{92,93} In SARS-CoV, four of six *in vitro* studies found an antiviral effect.^{14,64,89,94–96} However, no virological effects of ribavirin were found in SARS-CoV animal models when used as monotherapy.^{97,98} A mouse model even showed that ribavirin may prolong or enhance viral replication in the lungs.⁹⁹ Similarly in MERS-CoV, ribavirin is inhibitory but only at very high concentrations in Vero cells. The 50% inhibitory concentration (IC₅₀) of ribavirin was determined to be 41.45 μg/mL.⁷⁰ However, in humans, a level of only 24 μg/mL is achievable following a (high) 1000 mg intravenous dose.⁷⁰ Ribavirin monotherapy has not been studied in animal models for MERS-CoV.

Clinical data

In a systematic review of SARS treatment, 20/24 studies were deemed inconclusive due to inconsistent reporting of outcomes, an inconsistent treatment regimen, no control group or a biased control group. The effect of ribavirin could not be distinguished from the effects of other therapies such as corticosteroids and other antivirals.⁹¹ A single-centre RCT on SARS patients which compared ribavirin with IFN-1α showed no significant differences in days to symptom improvement and discharge.¹⁰⁰ Four

presented evidence of possible harm, including haemolytic anaemia, liver dysfunction and metabolic derangements.^{101–104}

Synergy between ribavirin and IFN is discussed under the section on IFNs above.

Mycophenolic acid

Similar to ribavirin, mycophenolic acid is an inhibitor of cellular inosine monophosphate dehydrogenase, and has antiviral activities against a number of viruses including influenza A.¹⁰⁵ Via the same mechanism, mycophenolic acid also inhibits purine nucleotide synthesis in lymphocytes.¹⁰⁶ This makes it a popular immunosuppressant in solid-organ transplants and autoimmune diseases such as systemic lupus erythematosus.

In vitro and animal studies

Although mycophenolic acid has no *in vitro* or murine effect on SARS-CoV, it inhibits MERS-CoV at a concentration achievable by standard clinical oral dosing.^{13,107} It displays synergy with IFN-β1b¹⁰⁷ and thiopurine analogues¹⁰⁸ *in vitro*. However, in common marmosets, mycophenolic acid-treated animals developed severe and/or fatal disease with higher mean viral loads (0.15–0.54 log₁₀ copies/glyceraldehyde 3-phosphate dehydrogenase; $P < 0.05$) than untreated animals.⁷³ The mortality rate at 36 h post-inoculation of MERS CoV was 67% (untreated and mycophenolic acid-treated) versus 0%–33% (lopinavir/ritonavir-treated and IFN-β1b-treated).

Clinical data

The use of mycophenolic acid monotherapy has not been reported in MERS. IFN-β and mycophenolic acid combination therapy was described in a retrospective observational study in Saudi Arabia involving 51 patients;³ all of the 8 patients who received IFN-β and mycophenolic acid survived. However, this group of patients had lower Acute Physiology and Chronic Health Evaluation II (APACHEII) scores compared with the rest who received a variety of antiviral agents including ribavirin and IFN-α, steroids and antibiotics.

Cyclosporin A

Cyclosporin and its derivatives inhibit the cellular peptidyl-prolyl isomerase activities of cyclophilins, which are important for the replication of viruses including HIV and hepatitis C virus.^{109–111}

Non-immunosuppressive cyclosporin DEBIO-025 (alisporivir) was found to be highly potent in hepatitis C treatment with a IC₅₀ for inhibition in Huh 5–2 cells of 0.27±0.03 μg/mL, compared with cyclosporine A's IC₅₀ of 2.8±0.4 μg/mL.¹¹² It was also found that a combination of IFN-α2a with either cyclosporine A or DEBIO-025 resulted in additive to slightly synergistic antiviral activity.¹¹²

In vitro activity

Low micromolar, non-cytotoxic concentrations of cyclosporin A strongly affected the replication of SARS-CoV and MERS-CoV in Vero and Huh7 cell cultures.^{13,67,113} Cyclosporin rendered SARS-CoV

RNA and protein synthesis almost undetectable, suggesting an early block in replication.¹¹³

Clinical data

There are no clinical data available on the efficacy of cyclosporin A in SARS or MERS. Cyclosporin A is readily available due to its use in solid-organ transplant patients and as therapy for autoimmune conditions such as rheumatoid arthritis and psoriasis. Its immune suppressive effect raises concern about the setting of infections, especially with a high EC_{50}/C_{max} ratio at standard therapeutic dosages.

Chloroquine

Chloroquine is an antimalarial that sequesters protons in lysosomes to increase intracellular pH.

***In vitro* and animal studies**

Chloroquine is inhibitory *in vitro* for multiple viruses including influenza, dengue virus and MERS-CoV at a concentration achievable by standard clinical oral dosing.^{11,114-116} However, it did not reduce viral replication in SARS-CoV infected mice, possibly because the cell surface pathway was not simultaneously blocked.⁶²

Clinical data

No clinical data are available on the efficacy of chloroquine on coronaviruses. Its use in seasonal prophylaxis for influenza was studied in a large RCT.¹¹⁷ Chloroquine was well tolerated but failed to prevent disease.

Nitazoxanide

Nitazoxanide is a potent type 1 IFN inducer that was originally developed as an antiprotozoal agent.¹¹⁸ It is being repurposed as a broad-spectrum antiviral agent, and is undergoing development for the treatment of hepatitis C, influenza and other viral respiratory infections. In addition to its antiviral activity, nitazoxanide inhibits the production of pro-inflammatory cytokines in peripheral blood mononuclear cells.¹¹⁹

***In vitro* activity**

Nitazoxanide possesses potent antiviral activity against influenza viruses,¹²⁰ and is one of the top three inhibitors that demonstrated robust anti-coronavirus activities in a recent screen of the NIH Clinical Collection library.¹²¹ It was shown to inhibit MERS CoV cultured in LLC-MK2 cells with an IC_{50} of 0.92 $\mu\text{g}/\text{mL}$, similar to the levels observed for influenza and other viruses. This IC_{50} is achievable in humans following twice daily administration of nitazoxanide extended-release tablets: peak and trough plasma concentrations were reported to be 4.6 and 0.8 $\mu\text{g}/\text{mL}$, respectively.¹¹⁹

Clinical data

There are no clinical data on the efficacy of nitazoxanide in SARS or MERS. There are two Phase 2 RCTs showing benefits in childhood

respiratory infections and uncomplicated influenza in adults, respectively.^{122,123}

Antibiotics

Broad-spectrum antibiotics are commonly used in the management of MERS for empirical treatment of severe community-acquired pneumonia, as well as ventilator-associated bacterial pneumonia. Teicoplanin, a glycopeptide antibiotic that inhibits bacterial cell wall synthesis, was recently found to have actions against MERS-CoV and Ebola virus.¹²⁴

In vitro

Teicoplanin was found to potently prevent the entry of MERS-CoV and SARS-CoV pseudotyped viruses into host cellular cytoplasm. Furthermore, teicoplanin has an inhibitory effect on replication-competent virus-like particles, with a low IC_{50} of 330 nM.¹²⁴

In vivo

Teicoplanin is clinically effective in the treatment of Gram-positive bacterial infections including *Enterococcus faecalis*, *Staphylococcus aureus* and *Streptococcus viridans*. Further pharmacodynamics studies specific to MERS-CoV are required to discern its antiviral efficacy.

Fusion inhibitors

***In vitro* and animal studies**

Analogous to the mechanism of mAbs, antiviral peptides target various regions of S protein to prevent MERS-CoV entry into host cells. Camostat, a serine protease inhibitor with a good safety profile used to treat chronic pancreatitis in humans, suppresses MERS-CoV entry into human bronchial submucosal gland-derived Calu-3 cells by 10-fold and virus growth by 270-fold.¹²⁵ However, it was found not to be efficacious against MERS-CoV infection of derived cells from immature lung tissue. Another type of fusion inhibitor under *in vitro* study is the heptad repeat 2 peptide (HR2P), a synthesized peptide derived from the HR2 domain of MERS-CoV S protein. It specifically binds to the HR1 domain of the viral S protein and blocks MERS-CoV replication and its S protein-mediated cell-cell fusion.¹²⁶ Intranasal administration of HR2P-M2 effectively protected adenovirus serotype-5-human dipeptidyl peptidase 4-transduced mice from infection by MERS-CoV strains with or without mutations in the HR1 region of S protein, with >1000-fold reduction of viral titres in lung. The protection was enhanced by combining HR2P-M2 with IFN- β .¹²⁷ Combining antiviral peptides targeting different regions of the S2 subunit of the S protein theoretically may overcome the risk of drug resistance.

Clinical data

Investigations of fusion inhibitors for MERS remain preclinical. There are no clinical data on the efficacy of fusion inhibitors in SARS or MERS.

Mannose-binding lectin

In vitro activity

Mannose-binding lectin (MBL) is a key molecule in innate immunity, and functions as an ante-antibody before the specific antibody response. MBL inhibits viral binding via SARS-CoV S glycoprotein.¹²⁸ A retrospective case-control study on the serum of 569 SARS patients and 1188 control subjects showed a higher frequency of haplotypes associated with low or deficient levels of MBL in SARS patients than in control subjects.¹²⁹ MBL deficiency is therefore a possible susceptibility factor for acquisition of SARS.

Clinical data

MBL remains an investigational therapy. There are no clinical data on the efficacy of MBL in SARS or MERS.

Corticosteroids

Corticosteroids were widely used in SARS due to their anti-inflammatory effects.^{74,101,130-136} Most of these cohorts were treated simultaneously with ribavirin. However, the potential local and systemic immunosuppression by corticosteroids is concerning.^{137,138} One RCT concluded that the administration of corticosteroids might enhance viral replication in the lung, as shown by higher plasma SARS-CoV viral load and slower serum viral clearance in weeks 2-3 of illness in patients given hydrocortisone ($n=10$) than in those given normal saline ($n=7$) in the early phase of the disease.¹³⁹ There were similar findings when corticosteroids were tested in H1N1 influenza-affected patients.¹⁴⁰ A retrospective cohort study showed that the use of corticosteroids was associated with increased risks of prolonged lower respiratory tract viral replication, nosocomial infections, ventilator-associated pneumonia and higher mortality.¹⁴⁰ Many patients with severe MERS were treated with systemic high-dose corticosteroids, which were intended to reverse the progression of respiratory distress and to prevent lung fibrosis. This has not proven to be successful.¹⁴¹ Corticosteroids do not improve longer-term outcomes in ARDS and their routine use is not recommended.¹⁴² In addition, corticosteroids were also associated with osteonecrosis, delirium and aspergillosis.¹⁴³⁻¹⁴⁶

Discussion

It is challenging to select appropriate pharmacological treatments when faced with a novel infection and inconclusive data drawn from many sources. Despite discovering a fairly large number of repurposed drugs that have activities against MERS-CoV, few have fulfilled their potential in clinical settings. Most of these agents have drawbacks, either in having high EC_{50}/C_{max} ratios at clinical dosages or immunosuppressive side effects, which discouraged further clinical trials. The sporadic epidemiology has also made patient recruitment into clinical trials difficult. The use of any therapeutics in MERS-CoV remains investigational. Data extrapolated from use in SARS, either *in vitro* or clinically, are, at best, of speculative value.

Convalescent plasma, IFN with or without ribavirin, and lopinavir/ritonavir are most likely to be beneficial and should be further evaluated. There are retrospective and non-randomized interventional

data obtained during the SARS and H1N1 outbreaks showing that convalescent plasma brought about a rapid decrease in viraemia and reduced mortality.^{18,43-51} Treatment with convalescent plasma is likely to be more effective when there is significant viraemia, hence early administration is key.^{51,52} A prospective human study investigating the use of convalescent plasma in MERS is ongoing, but is facing logistical and recruitment challenges. Plasma products and immunoglobulins vary geographically and will likewise vary in efficacy against MERS.⁵⁵⁻⁵⁷ Given the small number of MERS patients and the significant mortality of this infection, there may not be sufficient convalescent sera for this to be a scalable option, particularly outside of the Middle East. Cross-reactivity between SARS-CoV and MERS-CoV antibodies has been observed but is unlikely to be useful therapeutically.²² mAbs could offer a useful alternative as they are rapidly reproducible and have so far shown high potency and specificity. However, further development is likely to be tempered by the challenges of licensing and full-scale production at affordable costs for an undefined population.

IFN and ribavirin with or without lopinavir/ritonavir is the most reported therapy for MERS. Although non-human primate studies showed that combination treatment of IFN with ribavirin and/or lopinavir resulted in reduced virus replication, moderated host response and improved clinical outcome,^{72,73} five small-scale retrospective studies in critically ill patients failed to show mortality benefits.⁸⁰⁻⁸⁴ This discrepancy between *in vitro* and *in vivo* findings may be related to the high EC_{50}/C_{max} ratios of these drugs and delays in drug administration.^{13,70} Early drug administration is essential in MERS patients as they have a more rapid progression to death than SARS patients.¹⁴⁷ Ribavirin should be used with caution as *in vitro* studies for MERS-CoV required a high serum concentration for inhibition.^{70,72} The dose of ribavirin can be reduced when used together with IFN- $\alpha 2b$ ⁷⁰ but it is associated with multiple side effects including haemolysis, electrolyte imbalances and liver impairment, which can occur in up to 61% of treated patients.¹⁰² Lopinavir has been shown in limited observational studies to result in lower mortality and less progression to ARDS in SARS.^{89,90} Its use has been reported in one MERS patient, who cleared viraemia 2 days after administration of lopinavir/ritonavir, ribavirin and IFN- $\alpha 2a$.⁷⁶ Some have suggested that antiviral administration should be considered as soon as possible after diagnosis¹⁴⁸ based on limited clinical evidence that earlier administration of IFN and ribavirin resulted in a trend towards improved survival in MERS.⁸³ Similarly in SARS, therapeutic benefit was observed when ribavirin was given earlier than 6-14 days after the onset of symptoms.^{91,149}

Corticosteroids, ribavirin monotherapy and mycophenolic acid are likely to cause more harm than benefit. Corticosteroids cause local and systemic immunosuppression. Their administration has been associated with higher plasma viral load, slower viral clearance and higher mortality in both SARS and H1N1.^{138,139} Furthermore, they have not been shown to improve longer-term outcomes in ARDS.¹⁴² Ribavirin should not be considered for use as a monotherapy due to its poor side effect profile and the high dosage required to inhibit MERS-CoV.^{70,72} It has not been shown to be effective in MERS. In SARS, most of the clinical evidence on ribavirin was deemed inconclusive.⁹¹ There are no clinical data on the efficacy of mycophenolic acid in SARS or MERS. However, it led to severe and/or fatal disease with higher mean viral loads in an animal model.⁷³

While animal to human transmission of MERS CoV continues in the Middle East, it is likely that infected individuals will continue to export the illness to countries with minimal or no experience of dealing with it. Understanding the value and risks of the many treatment options is needed when urgently selecting a therapeutic regimen, especially during what will necessarily be a stressful and 'public' period for any host country and institution. The medical team will need to make decisions based on the body of available information, which gives anything but clear direction. Treatments will need to be applied adhering to research treatment protocols and systematic data collection. Meanwhile, as clinical researchers we simply must improve our ability to undertake multicentre, multinational RCTs in outbreak settings, particularly for emerging pathogens.

Transparency declarations

None to declare.

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