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A Systematic Review of therapeutic agents for the treatment of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

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ABSTRACT

Background: The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was first described in 2012 and attracted a great international attention due to multiple healthcare associated outbreaks. The disease carries a high case fatality rate of 34.5%, and there is no internationally or nationally recommended therapy.

Method: We searched MEDLINE, Science Direct, Embase and Scopus databases for relevant papers published till March 2019 describing in vitro, in vivo or human therapy of MERS.

Results: Initial search identified 62 articles: 52 articles were from Medline, 6 from Embase, and 4 from Science Direct. Based on the inclusions and exclusions criteria, 30 articles were included in the final review and comprised: 22 in vitro studies, 8 studies utilizing animal models, 13 studies in humans, and one study included both in vitro and animal model. There are a few promising therapeutic agents on the horizon. The combination of lopinavir/ritonavir and interferon-beta-1b showed excellent results in common marmosets and currently is in a randomized control trial. Ribavirin and interferon were the most widely used combination and experience comes from a number of observational studies. Although, the data are heterogenous, this combination might be of potential benefit and deserve further investigation. There were no randomized clinical trials to recommend specific therapy for the treatment of MERS-CoV infection. Only one such study is planned for randomization and is pending completion. The study is based on a combination of lopinavir/ritonavir and interferon-beta-1b. A fully human polyclonal IgG antibody (SAB-301) was safe and well tolerated in healthy individuals and this agent may deserve further testing for efficacy.

Conclusion: Despite multiple studies in humans there is no consensus on the optimal therapy for MERS-CoV. Randomized clinical trials are needed and potential therapies should be evaluated only in such clinical trials. In order to further enhance the therapeutic aroma for MERS-CoV infection, repurposing old drugs against MERS-CoV is an interesting strategy and deserves further consideration and use in clinical settings.

1. Introduction

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was first identified in 2012 and since then the disease has attracted an increasing international interest to resolve issues related to the epidemiology, clinical features, and therapy. This interest is further enhanced by the fact that MERS-CoV infection resulted in 2428 cases in 27 countries around the world as of June 23, 2019 [1] and most of the cases are linked to the Middle East [2]. So far there have been three patterns of the transmission of MERS-CoV virus mainly: sporadic cases [3], intra-familial transmissions [4–6] and healthcare-associated transmission [3,7–26]. The disease carries a high case fatality rate of 34.5% [1] and so far there has been no proven effective therapy and no approved therapies for MERS-CoV infection by international or national societies. Few therapeutic agents were reported in the literature but all were based on retrospective analysis. In this study, we review available literature on the current therapeutic options for the disease including in vitro, animal studies, and studies in human.

1.1. Search strategy

We searched four electronic databases: MEDLINE, Science Direct,
Embase and Scopus for articles in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]. We used the following terms:

#1: “Middle East Respiratory Syndrome Coronavirus” OR “MERS virus” OR “MERS Viruses” OR “MERS-CoV” OR “Novel Coronavirus” AND

#2: “Drug effect” OR “Drug Therapy” OR “Combination drug therapy” OR “Drug Ther*” OR “Combination drug ther*”

In addition, we reviewed the references of retrieved articles in order to identify additional studies or reports not retrieved by the initial search. The included studies were arranged as: in vitro studies, animal studies and human studies. We included studies conducted in the vitro, animal, or humans that measured the impact of drug therapy against MERS-CoV. We excluded studies that examined the impact of drug therapy against Coronavirus other than MERS-CoV, any study that focused on drug synthesis and extractions, review articles, studies of supplemental therapy, and articles focused on the mechanism of action of medications.

2. Results

Initial search identified 62 articles: 52 articles were from Medline, 6 articles from Embase, and 4 articles from Science Direct. Of those, 32 studies were excluded: review studies (n = 16), drug synthesis and extraction (n = 3), supplemental therapy (n = 1), drug therapy in Coronavirus in general (n = 4), and site of action of different drugs modalities (n = 8). Based on the inclusions and exclusions criteria, only 30 articles were included in the final review: 13 studies were conducted in vitro, 8 studies were done in animal models, 8 studies were done in humans, and one study included both in vitro and animal model (Fig. 1).

2.1. In vitro studies

There were many in vitro studies evaluating various agents against MERS-CoV such as: interferon (INF), ribavirin, and HIV protease inhibitors (nelfinavir, ritonavir and lopinavir) as summarized in Table 1. In vitro studies showed that IFN-β has a lower 50% inhibitory concentration ($IC_{50}$) for MERS-CoV compared with IFN-α2b [28]. In addition, IFN-β has a superior anti-MERS-CoV activity in the magnitude of 16-, 41-, 83- and 117-fold higher compared to IFN-α2b, IFN-γ, IFN-universal type 1 and IFN-α2a, respectively [28]. Pegylated Interferon-α (PEG-IFN-α) inhibited the effect of MERS-CoV at a dose of 1 ng/ml with complete inhibition of cytopathic effect (CPE) at doses of 3–1000 ng/ml in MERS-CoV infected Vero cells [29].

Ribavirin, a nucleoside analog requiring activation by host kinases to a nucleotide, required high in vitro doses to inhibit MERS-CoV replications and these doses are too high to be achieved in vivo [30,31]. The combination of interferon-α2b (INF-α2b) and ribavirin in Vero cells resulted in a an 8-fold reduction of the IFN-α2b dose and a 16-fold reduction in ribavirin dose [30].

The HIV protease inhibitors, Nelfinavir and lopinavir, were thoughts to inhibit MERS-CoV based on results from SARS [32]. Nelfinavir mexitylate hydrate and lopinavir showed suboptimal 50% effective concentration ($EC_{50}$) in the initial CPE inhibition assay and were not evaluated further [31]. In another study, the mean $EC_{50}$ of lopinavir using Vero E6 and Huh7 cells was 8.0 μM [33].

MERS-CoV requires fusion to the host cells to replicate, thus MERS-CoV fusion inhibitors such as camostat and the Heptad Repeat 2 Peptide (HR2P) were evaluated in vitro [34,35]. Camostat inhibited viral entry into human bronchial submucosal gland-derived Calu-3 cells but not immature lung tissue [34]. HR2P was shown to inhibit MERS-CoV replication and the spike protein-mediated cell-cell fusion [35]. Camostat was effective in reducing viral entry by 15-folds in the Vero-TMPRSS2 cells infected with MERS-CoV [36].

Nitazoxanide, a broad-spectrum antiviral agent, and teicoplanin, an
| Study type            | Cell Type                         | Treatment                   | Outcome                                                                                                                                 |
|----------------------|-----------------------------------|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| [29] In vitro Comparator study | MERS-CoV infected Vero cells and mock-infected Huh7 cells. | Cyclosporin 3μg, DMSO (a solvent control) | CPE inhibited and no change on the cell viability on the infected Vero cells compared with mock-infected cells                           |
|                      |                                   |                             | CPE reduced or inhibited by 7.5 μg and 15 μg Cyclosporine.                                                                            |
|                      |                                   |                             | No change in CPE                                                                                                                      |
|                      |                                   |                             | CPE reduced at 1 ng/ml and complete inhibition at doses 3, 10, 30, 100, 300, or 1000 ng/ml.                                            |
|                      |                                   |                             | Genome copies reduced by 0.53-log at 500 U/ml and highest reduction by 1.84-log at 5000 U/ml.                                            |
|                      |                                   |                             | Viral titer reduced by 0.57-log at 500 U/ml and highest reduction by 1.31-log at 5000 U/ml.                                            |
|                      |                                   |                             | IC50 = 58.08 U/ml, IC90 = 320.11 U/ml, and IC99 = 2061.89 U/ml.                                                                     |
|                      |                                   |                             | Reduced viral protein level with increased dose starting at 250 U/ml.                                                                 |
|                      |                                   |                             | Viral titer reduced below the detection threshold of 13.7 TICD50/ml at 200 μg/ml.                                                   |
|                      |                                   |                             | EC50 = 12.9 μM with no virus reduction                                                                                               |
| [30] In vitro Comparator study | hCoV-EMC infected Vero cells     | INF-α2b, Ribavirin + INF-α2b | Virus reduction by 3.1 log10 if dose > 15 μM                                                                                           |
|                      |                                   |                             | No virus reduction                                                                                                                    |
|                      |                                   |                             | Dose treated too low to determine EC50 with high cytotoxicity.                                                                          |
|                      |                                   |                             | Virus reduction by 1-1.5 log10 if dose > 20 μM with increased in the toxicity.                                                          |
|                      |                                   |                             | EC50 = 33.58 μM with high cytotoxicity CC90 = 25.64 μM, SI was 1.9                                                                    |
|                      |                                   |                             | Virus reduction by 2 logEC50 with narrow therapeutic window and high toxicity                                                           |
|                      |                                   |                             | Virus reduction by 1-1.5 log10 if dose > 20 μM with increased in the toxicity.                                                          |
|                      |                                   |                             | No antiviral activity and no cytotoxicity.                                                                                        |
|                      |                                   |                             | Virus reduction by 2 logEC50 with narrow therapeutic window and high toxicity                                                           |
|                      |                                   |                             | No antiviral activity and no cytotoxicity.                                                                                        |
|                      |                                   |                             | Chloroquine: dose-dependent, EC50 = 3.0 ± 1.1 μM and CC90 = 58.1 ± 1.1 μM, SI was 19.4                                         |
|                      |                                   |                             | Chloroquine: Complete inhibition at 12 μM, EC90 = 4.9 ± 1.2 μM and                                                             |
|                      |                                   |                             | Chloropromazine: Complete inhibition at 12 μM, EC90 = 4.9 ± 1.2 μM and                                                             |
|                      |                                   |                             | Chloropromazine: Complete inhibition at 12 μM, EC90 = 4.9 ± 1.2 μM and                                                             |
|                      |                                   |                             | Chloropromazine: Complete inhibition at 12 μM, EC90 = 4.9 ± 1.2 μM and                                                             |
|                      |                                   |                             | Chloropromazine: Complete inhibition at 12 μM, EC90 = 4.9 ± 1.2 μM and                                                             |
|                      |                                   |                             | Chloropromazine: Complete inhibition at 12 μM, EC90 = 4.9 ± 1.2 μM and                                                             |
|                      |                                   |                             | Chloropromazine: Complete inhibition at 12 μM, EC90 = 4.9 ± 1.2 μM and                                                             |
|                      |                                   |                             | Chloropromazine: Complete inhibition at 12 μM, EC90 = 4.9 ± 1.2 μM and                                                             |
|                      |                                   |                             | Chloropromazine: Complete inhibition at 12 μM, EC90 = 4.9 ± 1.2 μM and                                                             |
|                      |                                   |                             | Virus reduction by 1-1.5 log10 if dose > 20 μM with increased in the toxicity.                                                          |
|                      |                                   |                             | No antiviral activity and no cytotoxicity.                                                                                        |
|                      |                                   |                             | Virus reduction by 2 logEC50 with narrow therapeutic window and high toxicity                                                           |
|                      |                                   |                             | No antiviral activity and no cytotoxicity.                                                                                        |
|                      |                                   |                             | Virus reduction by 2 logEC50 with narrow therapeutic window and high toxicity                                                           |
|                      |                                   |                             | No antiviral activity and no cytotoxicity.                                                                                        |
|                      |                                   |                             | Loperamide: Complete inhibition at 8 μg, EC90 = 4.8 ± 1.5 μM and CC90 = 15.5 ± 1.0 μM, SI was 3.2                          |
|                      |                                   |                             | Lopinavir: Complete inhibition at 12 μM, EC90 = 8 ± 1.5 μM and CC90 = 24.4 ± 1.0 μM, SI was 3.1                          |
|                      |                                   |                             | Lopinavir: Complete inhibition at 12 μM, EC90 = 8 ± 1.5 μM and CC90 = 24.4 ± 1.0 μM, SI was 3.1                          |
|                      |                                   |                             | Lopinavir: Complete inhibition at 12 μM, EC90 = 8 ± 1.5 μM and CC90 = 24.4 ± 1.0 μM, SI was 3.1                          |
|                      |                                   |                             | Lopinavir: Complete inhibition at 12 μM, EC90 = 8 ± 1.5 μM and CC90 = 24.4 ± 1.0 μM, SI was 3.1                          |
|                      |                                   |                             | Lopinavir: Complete inhibition at 12 μM, EC90 = 8 ± 1.5 μM and CC90 = 24.4 ± 1.0 μM, SI was 3.1                          |
|                      |                                   |                             | Lopinavir: Complete inhibition at 12 μM, EC90 = 8 ± 1.5 μM and CC90 = 24.4 ± 1.0 μM, SI was 3.1                          |
|                      |                                   |                             | Lopinavir: Complete inhibition at 12 μM, EC90 = 8 ± 1.5 μM and CC90 = 24.4 ± 1.0 μM, SI was 3.1                          |
|                      |                                   |                             | Lopinavir: Complete inhibition at 12 μM, EC90 = 8 ± 1.5 μM and CC90 = 24.4 ± 1.0 μM, SI was 3.1                          |
|                      |                                   |                             | Lopinavir: Complete inhibition at 12 μM, EC90 = 8 ± 1.5 μM and CC90 = 24.4 ± 1.0 μM, SI was 3.1                          |
|                      |                                   |                             | Lopinavir: Complete inhibition at 12 μM, EC90 = 8 ± 1.5 μM and CC90 = 24.4 ± 1.0 μM, SI was 3.1                          |
|                      |                                   |                             | Lopinavir: Complete inhibition at 12 μM, EC90 = 8 ± 1.5 μM and CC90 = 24.4 ± 1.0 μM, SI was 3.1                          |
|                      |                                   |                             | Lopinavir: Complete inhibition at 12 μM, EC90 = 8 ± 1.5 μM and CC90 = 24.4 ± 1.0 μM, SI was 3.1                          |
|                      |                                   |                             | Lopinavir: Complete inhibition at 12 μM, EC90 = 8 ± 1.5 μM and CC90 = 24.4 ± 1.0 μM, SI was 3.1                          |

(continued on next page)
| Study type                      | Cell Type                              | Treatment                        | Outcome                                                                 |
|--------------------------------|----------------------------------------|----------------------------------|--------------------------------------------------------------------------|
| [44] In vitro Comparator study | Huh-7 cells infected with MERS-CoV      | Saracatinib                      | MERS-CoV infected cells: EC<sub>50</sub> = 2.9 μM and CC<sub>50</sub> > 50 μM, SI > 17, \n|                                |                                        |                                 | Dose 1 μM viral titer reduced by > 50% (P < 0.05) with no effect on viral N protein after 24 h \n|                                |                                        |                                 | Dose 10 μM: viral titer reduced by 90% (P < 0.05) with complete depletion on the viral N protein after 24 h \n|                                |                                        |                                 | Complete inhibition of viral genomic RNA and mRNA synthesis (P < 0.0001) \n|                                |                                        |                                 | Viral titer: \n|                                |                                        |                                 | Pretreatment: no difference \n|                                |                                        |                                 | At time of infection: marked reduction with significant a decrease of viral genomic RNA and mRNA synthesis. \n|                                |                                        |                                 | Post treatment (within 2 h): complete inhibition (P < 0.0001) \n|                                |                                        |                                 | Post treatment (after 4 h): less effect (P < 0.05) \n|                                |                                        |                                 | rMERS-CoV infected cells: EC<sub>50</sub> = 9.3 μM \n|                                |                                        |                                 | Huh-7 cells infected with rMERS-CoV \n|                                |                                        |                                 | E<sub>50</sub> = 1.2 μM with complete viral depletion at dose ≥ 1 μM \n|                                |                                        | Synergistic effect at combination index of 0.529 \n|                                |                                        |                                 | Cytotoxicity: no difference compared with Saracatinib and less compared with Gemcitabine \n|                                |                                        |                                 | Reduced cell death at 125–250 μM (MTS assay P < 0.05, neutral red uptake assay P < 0.005) \n|                                |                                        |                                 | Less cytotoxicity even at higher concentration \n|                                |                                        |                                 | Viral RNA level: \n|                                |                                        |                                 | At concentration 31.25–250 μM: after 48 h lower than after 24 h \n|                                |                                        |                                 | After 48 h at concentration 150 μM: lower (P < 0.05), at concentration 200 μM (P < 0.01), at concentration 250 μM (P < 0.001). \n|                                |                                        |                                 | If the drug added at time of infection: no difference in the cell proliferations and viral titers. \n|                                |                                        |                                 | After 24 h, the inhibition of N protein is dose dependent manner. \n|                                |                                        |                                 | At concentration 150 μM: limited decrease in the N protein \n|                                |                                        |                                 | At concentration 250 μM: elimination of N protein \n|                                |                                        |                                 | Inhibited Caspase 3 cleavage: dose dependent manner. \n|                                |                                        |                                 | If drug administered consecutively at lower dose: \n|                                |                                        |                                 | Ever 24 h, dose ≤ 62.5 μM: the cell proliferation and cells viability were higher compared with untreated group (P < 0.001). The cytotoxicity and viral titer were lower (P < 0.001) \n|                                |                                        |                                 | GS-41524: EC<sub>50</sub> = 0.86 μM \n|                                |                                        |                                 | Remdesivir: EC<sub>50</sub> = 0.074 μM \n|                                |                                        |                                 | More reduction in viral titer if the drug were added 24-72 h post infection \n|                                |                                        |                                 | Significant reduction in the viral replication and dsRNA level \n|                                |                                        |                                 | IC<sub>50</sub> = 5 μg/ml \n|                                |                                        |                                 | > 95% reduction at concentration > 25 μg/ml \n|                                |                                        |                                 | (continued on next page) \n|}
| Study type | Cell Type | Treatment | Outcome |
|------------|-----------|-----------|---------|
| In vitro Comparator study | Vero-TMPRSS2 infected cells | Camostat | At dose 10µM, decreased viral entry by 15-fold |
| | Vero-TMPRSS2- negative infected cells | Camostat | At dose 10µM, no effect on the viral entry |
| | Calu-3 cells | Camostat | At dose 10µM, decreased viral entry by 10-fold |
| | MRC-5 cells or WI-38 cells | Camostat | Viral RNA suppressed by 90-fold |
| | Vero-TMPRSS2 infected cells | EST (an inhibitor of endosomal cathepsins) | At dose 10µM, slight inhibition of viral entry |
| | Vero-TMPRSS2- negative infected cells | EST (an inhibitor of endosomal cathepsins) | At dose 10µM, inhibit viral entry |
| | Calu-3 cells | Camostat + EST (an inhibitor of endosomal cathepsins) | Decreased viral entry by 180-fold |
| | MRC-5 cells | Single treatment + Leupeptin | No significant difference in the viral entry |
| | WI-38 cells | Cathepsin 1 inhibitor | Inhibit the viral entry by 40-fold |
| | Vero-TMPRSS2- negative infected cells | Cathepsin K inhibitor | No effect on the viral entry |
| | Calu-3 cells | Cathepsin S inhibitor | Dose dependent effect |
| | MRC-5 cells | Leupeptin | Blocked viral entry at 10–100 µM |
| | WI-38 cells | Leupeptin | No effect on the viral entry |
| In vitro Comparator study | Vero E6 cells infected with MERS-CoV | Chlorpromazine | $EC_{50} = 9.51 \mu M$ with low toxicity |
| | | Trifluromazine | $EC_{50} = 5.76 \mu M$ with low toxicity |
| | | Imatinib | $EC_{50} = 14.69 \mu M$ with low toxicity |
| | | Dasatinib | $EC_{50} = 5.47 \mu M$ with low toxicity |
| | | Nilotinib | No significant inhibition of MERS-CoV |
| | | Gemcitabine | $EC_{50} = 1.23 \mu M$ with low toxicity |
| | | Toremifene | $EC_{50} = 12.92 \mu M$ with low toxicity |

* CPE: cytopathic effect; PEG-INF: pegylated interferon; INF: interferon; IC50: inhibitory concentration of 50% of cells; IC90: inhibitory concentration of 90% of cells; IC99: inhibitory concentration of 99% of cells; EC50 and EC90: 50% and 90% maximal effective concentration; CC50: cytotoxicity concentration that kills 50% of cells; RT-qPCR: Real time Quantitative polymerase chain reaction;
A summary of the use of anti-viral agents for the treatment of MERS-CoV infection in animal model.

| Study type                  | Total #     | Supportive therapy | Treatment plan                                                                 | Outcome                                                                 |
|-----------------------------|-------------|--------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Comparator trial Rhesus monkey | No          |                    | 3B11-N antibody, 4E10-N antibody, or no treatment 1 day before inoculation (prophylaxis) | Less abnormal lung volume and less lung pathology                       |
| Comparator trial hDPP4-Tg mice | No          |                    | After 1 day of inoculation IV hMS-1 2 mg/kg versus Trastuzumab (Treatment)      | bMS-1 vs Trastuzumab: <ul><li>Less viral titer</li><li>Less lung injury</li><li>Fewer histopathological changes</li><li>Less decrease in the body weight</li><li>More survival rate</li></ul> Decreased viral titer |
| Comparator trial Ad5-hCD26- transduced mice | No          |                    | Either 1 d before or 1 d after inoculation IV mAb 4C2b (Prophylaxis and treatment) | Decreased viral titer in all treated group compared with the control group with complete clearance in mice which received combination treatment. |
| Comparator trial Rhesus macaques | No          |                    | Treatment group (#3): INF-α-2a SQ + Ribavirin IV No treatment group (#3) | Decreased in oxygen saturation, increased white blood cells and neutrophils on day one more in no treatment | Chest radiograph in the treated group showed light infiltration in a single lobe by day 2, and 3. Decrease viral load in treatment group. Untreated groups: increased in perivascular infiltrates. |
| Comparator trial Ad5-hCD26- transduced mice | No          |                    | Treatment group: Intranasal peptide HR2P-M2 200 mcg 6 h before inoculation (Prophylaxis) | Decreased viral titer                                                                                                          |
| Comparator trial hDPP-4 Tg mice | No          |                    | 1st gp: 200 mcg intranasal HR2P-M2 2nd gp: 2000 U intranasal INF-β 3rd gp: Combination 4th gp: no treatment 6 h before inoculation (prophylaxis) | Viral inhibition in all treated group with the greatest reduction in the combination group HR2P-M2 alone vs INF-β alone. Reduced histopathologic change in INF-β and HR2P-M2 treated group with the greatest reduction in the combination group Better survival rate |
| Comparator trial 12 healthy common Marmosets | No          |                    | 1st gp: NMs10-Fc single dose 2nd gp: Trastuzumab Before inoculation (prophylaxis) 1st gp: NMs10-Fc single dose 2nd gp: Trastuzumab 3d after inoculation (treatment) | Better survival rate Steady weight compared with sharply decreased in the weight on the control group Better survival rate Less weight loss |
| Comparator trial Ad5-hDPP4- transduced mice | No          |                    | 1st gp: Intraperitoneal 100 or 500 mcg (5 or 25 mg/kg) of SAB-301 2nd gp: negative control Te hlgG 500 mcg 3rd gp: no treatment 12 h before inoculation (prophylaxis) 1st gp: intraperitoneally single dose 500 mcg SAB-301 antibody 2nd gp: intraperitoneally single dose Te hlgG 3rd gp: no treatment 1–2 h of inoculation (Treatment) | The viral titer was lowest in the 500 mcg vs Tc hlgG group and control group with the greatest reduction in the combination group. | Decreased Viral titer |

* Comparator trial hDPP4-Tg mice No 1st gp: no treatment 2nd gp: negative control Tc hIgG 500 mcg 3rd gp: no treatment 12 h before inoculation (prophylaxis) 1st gp: intraperitoneally single dose 500 mcg SAB-301 antibody 2nd gp: intraperitoneally single dose Te hlgG 3rd gp: no treatment 1–2 h of inoculation (Treatment)

 Comparator trial Ad5-hCD26- transduced mice No 1st gp: 200 mcg intranasal HR2P-M2 2nd gp: 2000 U intranasal INF-β 3rd gp: Combination 4th gp: no treatment 6 h before inoculation (prophylaxis) 1st gp: 200 mcg intranasal HR2P-M2 2nd gp: 2000 U intranasal INF-β 3rd gp: Combination 4th gp: no treatment 12 and 36 h after inoculation (treatment) 1st gp: NMs10-Fc single dose 2nd gp: Trastuzumab Before inoculation (prophylaxis) 1st gp: NMs10-Fc single dose 2nd gp: Trastuzumab 3d after inoculation (treatment) 1st gp: no treatment 2nd gp: intraperitoneally single dose 500 mcg SAB-301 antibody, 4E10-N antibody, or no treatment 1 day before inoculation (prophylaxis).

| Comparator trial Ad5-hCD26- transduced mice | No          |                    | 1st gp: Intraperitoneal 100 or 500 mcg (5 or 25 mg/kg) of SAB-301 2nd gp: negative control Te hlgG 500 mcg 3rd gp: no treatment 12 h before inoculation (prophylaxis) 1st gp: intraperitoneally single dose 500 mcg SAB-301 antibody 2nd gp: intraperitoneally single dose Te hlgG 3rd gp: no treatment 1–2 h of inoculation (Treatment) | Decreased in oxygen saturation, increased white blood cells and neutrophils on day one more in no treatment | Chest radiograph in the treated group showed light infiltration in a single lobe by day 2, and 3. Decrease viral load in treatment group. Untreated groups: increased in perivascular infiltrates. |
| Comparator trial hDPP-4 Tg mice | No          |                    | 1st gp: 200 mcg intranasal HR2P-M2 2nd gp: 2000 U intranasal INF-β 3rd gp: Combination 4th gp: no treatment 6 h before inoculation (prophylaxis) 1st gp: 200 mcg intranasal HR2P-M2 2nd gp: 2000 U intranasal INF-β 3rd gp: Combination 4th gp: no treatment 12 and 36 h after inoculation (treatment) 1st gp: NMs10-Fc single dose 2nd gp: Trastuzumab Before inoculation (prophylaxis) 1st gp: NMs10-Fc single dose 2nd gp: Trastuzumab 3d after inoculation (treatment) 1st gp: no treatment 2nd gp: intraperitoneally single dose 500 mcg SAB-301 antibody, 4E10-N antibody, or no treatment 1 day before inoculation (prophylaxis). |
| Comparator trial 12 healthy common Marmosets | No          |                    | 1st gp: no treatment 2nd gp: Mycophenolate mofetil intraperitoneal after 8 h of inoculation 3rd gp: + Ritonavir PO at 6, 30, and 54 h after inoculation, 4th gp: INF-β-1b SQ at 8 and 56 h post inoculation. (Treatment) | Lopinavir/Ritonavir and INF-β-1b have a better clinical score, less weight reduction, less radiological and pathological finding, and lower viral load in the lung and in the extrapulmonary The Mycophenolate has a higher viral load vs control group. The fatality rate was higher in untreated, and Mycophenolate vs treated groups |
| Comparator trial Ad5-hDPP4- transduced mice | No          |                    | 1st gp: Intraperitoneal 100 or 500 mcg (5 or 25 mg/kg) of SAB-301 2nd gp: negative control Te hlgG 500 mcg 3rd gp: no treatment 12 h before inoculation (prophylaxis) 1st gp: intraperitoneally single dose 500 mcg SAB-301 antibody, 4E10-N antibody, or no treatment 1 day before inoculation (prophylaxis). | The viral titer was lowest in the 500 mcg vs Te hlgG group at day 1 The viral titer was lowest in the 500 mcg vs Te hlgG and control group |

* mAb: monoclonal antibodies; INF: interferon; gp: group;

Toremifene, Chlorpromazine, and Chloroquine were evaluated using Vero cells, human monocyte-derived macrophages (MDMs) and immature dendritic cells (MDDCs) [41]. These drugs were transferred to cells 1 h prior to infection with MERS-CoV. After 48 h, viral replication was inhibited by Toremifene with 50% effective concentration (EC50) of 12.9 μM but the MDMs dose was too low to have a calculated EC50. Chlorpromazine inhibited MERS-CoV in Vero cells with an EC50 of 9.5 μM and no cytotoxicity. In MDMs cells, the EC50 was 13.8 μM with high 50% cytotoxicity concentration (CC50) of 25.64 μM. Chloroquine showed no antiviral activity in the MDMs. Toremifene reduced virus by 1–1.5 log10 at a dose more than 20 μM Chlorpromazine reduced MERS-CoV by 2 log10 and had a narrow therapeutic window and a high toxicity [41].

inhibitor of Cathepsin L in the Late Endosome/Lysosome cycle and a blocker of the entry of MERS-CoV, showed inhibitory effects of MERS-CoV in vitro [37,38].

The ability of recombinant receptor-binding domain (RBD-Fd) to inhibit MERS-CoV has been studied in DPP-4 expressing Huh-7 infected cells. The 50% inhibition dose (ID50) for RBD-Fd was 1.5 μg/ml compared with no inhibitory activity in untreated cells even at highest dose [39].

Cyclosporin affects the function of many cyclophilins that act as chaperones and facilitate protein folding [29,40]. In vitro, cyclosporine inhibited MERS-CoV replication [29,40]. Three days post infection, cytopathic effects (CPE) of MERS-CoV was inhibited by Cyclosporine Vero cells and mock-infected Huh7 cells [29].
Chloroquine, Chlorpromazine, and loperamide were tested on Huh7 cells [43]. The cells were treated 1-h prior to infection. Antiviral activity of chloroquine was dose-dependent. Chlorpromazine showed activity against MERS-CoV with EC50 of 4.9 ± 1.2 μM and CC50 of 21.3 ± 1.0 μM. Loperamide, an anti-diarrheal drug, inhibited MERS-CoV and induced CPE. Two kinase signaling (AB1L) pathway inhibitors (Imatinib mesylate and Dasatinib) were active against MERS-CoV in vitro [42]. In Vero E6 and MRC5 cells imatinib had a dose dependent killing [43].

Saracatinib has a broad-spectrum antiviral activity against different strain of MERS-CoV. After 72 h of infection of Huh-7 cells, Saracatinib exhibited an EC50 of 2.9 μM and CC50 of more than 50 μM [44]. Whereas, gemcitabine was shown to be effective against MERS-CoV infected Huh-7 cells with an EC50 of 1.2 μM and a complete viral depletion at a dose of ≥ 1 μM [44]. Inhibitory effect of resveratrol against MERS-CoV was tested using infected Vero E6 cells. After 48 h, cell death was significantly reduced in the treatment group with resveratrol. The study showed that resveratrol inhibited MERS-CoV after entry in the cells and when resveratrol was added at same time of MERS-CoV, there was no difference in cell proliferations and viral titers compared with cells treated after infections [45].

The antiviral activity of GS-441524 and its co-drug GS-5734 (Remdesivir) were tested on MERS-CoV infected human airway epithelial cell (HAE) [46]. GS-441524 has a mean EC50 of 0.86 μM and GS-5734 has a mean EC50 of 0.074 μM with more reduction in viral titer if the drug was added 24–72 h post infection [46].

Utilizing HAE cells infected with MERS-CoV, there was a significant reduction in viral replication and dsRNA level when cells were treated with K22 compound [47]. A novel peptide (P9) showed an in vitro activity against MERS-CoV at an IC50 of 5 μg/ml and more than 95% infection reduction at concentration higher than 25 μg/ml [48]. The two neurotransmitter antagonists (Chlorpromazine hydrochloride and trifluromazine hydrochloride) inhibit MERS-CoV infected Vero E6 cells [42]. The DNA synthesis and repair inhibitor, Gemcitabine Hydrochloride, and an Estrogen receptor I antagonist, Toremifene citrate, had antiviral activity against MERS-CoV [42]. An Estrogen receptor I antagonist, Toremifene citrate, had activity against MERS-CoV [42]. In addition, MERS-CoV is inactivated by amotosalen and ultraviolet light in fresh frozen plasma [49].

2.2. Animal studies

Monoclonal antibodies against SARS-CoV had been tested in animal models of MERS-CoV infection (Table 2). The monoclonal antibodies, 3B11-N and 4E10-N, were compared with no treatment in Rhesus Monkey model [50]. Antibodies, 3B11-N, were administered as a prophylaxis one-day prior to animal inoculation and showed significant reduction in lung disease radiographically. However, there was no significant difference when 3B11-N and 4E10-N were compared in term of lung pathology (P = 0.1122) [50].

Interferon alfa-2a in conjunction with ribavirin were tested in rhesus macaques model of MERS-CoV infection. The animals were randomly assigned to either treatment or control groups and therapy was started 8 h post-infection. Necropsy showed a normal appearance of the lung in the treatment group compared with the control group. Virus replication was significantly reduced in the lung of treated animal. Serum interferon alfa was 37 times the level in untreated group by day 2. In addition, the treated group showed reduced systemic and local levels of pro-inflammatory markers such as interleukin-2, monocyte chemoattractant protein-1, interleukin-2 receptor antagonist, interleukin-6, interleukin-15, and interferon-gamma [51].

Another study was conducted utilizing 12 healthy common marmosets inoculated with MERS-CoV and then assigned to four groups (control group; Mycophenolate mofetil intraperitoneally 8 h after inoculation; Lopinavir with Ritonavir at 6, 30, and 54 h after inoculation; or Interferon- Beta-1b subcutaneous at 8- and 56-h post inoculation) [52]. Lopinavir/Ritonavir and Interferon-beta-1b treated groups had better clinical scores, less weight reduction, less pulmonary infiltrate, and lower viral load than the untreated group. The Mycophenolate group had a higher viral load with severe disease compared with the control group. The fatality rate was higher than untreated, and Mycophenolate treated groups (67%) than Lopinavir/Ritonavir treated and Interferon-Beta-1 b treated groups (0–33%) after 36 h of inoculation [52].

The human dipetidyl peptidase-4 (DPD4) is a receptor for cell binding and entry of MERS-CoV. A transgenic mouse model with DPD4 was utilized to test the effects of humanized mAb (hMS-1). In the model, a single dose of hMS-1 protected the transgenic mouse from MERS-CoV infection and all control mice died ten days post-infection [53].

The Humanized antibodies mAb 4C2h are mouse-derived neutralizing spike receptor-binding domain of MERS-CoV (MERS-RBD) that were further humanized [54]. A single intravenous dose was injected one day pre and post MERS-CoV inoculation and showed that h-mAb 4C2h significantly decreased viral titer in the lungs in the mouse model (p < 0.05) [54].

Another study was done on adenoviruses expressing DPD4 in mouse lungs (Ad5-hDP4- Transduced mice) utilizing intranasal peptide derived from the heptad repeat (HR) 2 domain in S2 subunit known as HR2P analogue (HR2P-M2) [55]. The animals were either given intranasal HR2P-M2 6 h before infections or a control group with no treatment. The treated group showed decreased in the viral titer compared with the control group. The combination of HR2P-M2 with interferon β showed further reduction of infection [55].

The human-Fc fused version of neutralizing nanobody (NbMS10-Fc) was tested using hDPD4- transgenic mice model of MERS-CoV infection. The mice were injected with a single dose NbMS10-Fc or Trastuzumab (control group) before a lethal dose of MERS-CoV. The treatment group had a 100% survival rate compared with 0% survival rate in the control group [56].

The impact of a trans-chromosomal (Tc) bovine, fully human polyclonal immunoglobulin G (IgG) antibodies were tested on Ad5-hDP4-transduced mice five days after transduction and 12 h before inoculated MERS-CoV. Animals received either intraperitoneal SAB-301 or control or Tc hIgG group. Viral load was lower in mice treated with SAB-301 at day 1 and 2 post-infection [57].

A recombinant trimeric receptor-binding protein (RBD-Fd) was tested on hDPD4 transgenic mice infected with MERS-CoV. The animals received RBD-Fd subcutaneously and were boosted at 3 weeks, 6 weeks, and 6 months. RBD-Fd induced S1-specific IgG antibodies against MERS-CoV and was maintained for at least 6 months. The survival rate in RBD-Fd immunized mice was 83% [39].

2.3. Human studies

A summary of the use of different therapeutic agents in human is shown in Table 3. The first use of antiviral agents to treat MERS-CoV infection was observed in 5 patients in 2013 in Saudi Arabia [58]. All patients received ribavirin orally and subcutaneous interferon alfa-2b. Unfortunately, all patients died at 1–2 months due to respiratory and multi-organ failure and four patients experienced adverse drug reaction such as thrombocytopenia, anemia and pancreatitis [58].

In 2015, two patients with MERS-CoV infection in Kuwait were treated with pegylated interferon alfa-2b subcutaneously and oral ribavirin [59]. One patient was discharged home after 42 days of starting antiviral therapy and ribavirin was stopped after one week of therapy due to anemia. The second patient recovered from MERS-CoV and he subsequently died two months later with multidrug-resistant organism [59].

A large retrospective cohort study included 44 adult patients. Of those patients, 24 patients (control group) did not receive antiviral treatment, and 20 patients received subcutaneous pegylated interferon...
alfa-2a and oral ribavirin [60] per previously developed protocol [61]. The survival rate after 14 days from the date of diagnosis was statistically higher in the treatment group compared with the control group (70% versus 29%; P = 0.004). However, the survival rate did not differ in the two groups at 28 days (30% versus 17%; P = 0.054) [60].

In 2014, a retrospective cohort study was conducted on 24 confirmed MERS cases in Jeddah, Saudi Arabia and were started on day one of MERS-CoV confirmation [62]. Of those patients, 13 received interferon α-2a subcutaneous per week and 11 patients received interferon β-1a subcutaneous three times weekly. Both groups also received ribavirin orally. The case fatality rate was 85% in INF-α-2a versus 64% in INF-β-1a (p = 0.24). The fatality rate in patients using INF with positive MERS-CoV RT-PCR was 90% versus 44% in those with negative MERS-CoV RT-PCR test [62].

In 2015, pegylated interferon-α-2b and ribavirin was given to two confirmed cases in Riyadh. One patient was treated with PegIFN-α-2b and ribavirin and start to improve day 6 and had complete recovery at day 18. The second case was not a confirmed case and was started on these medication as a prophylaxis. On the fourth day, the patient started to improve and was discharged home after two weeks [63]. The combination therapy was also used in other case reports (Table 3) [64,65].

In a large cohort study of 51 patients, various combinations of interferon and ribavirin were used with different outcomes (Table 3) [66]. Another small study utilized ribavirin and interferon-alfa 2b in three patients who received therapy within 1–2 days of admission and were compared to three other patients who received therapy 12–19 days after admission [67]. The first group survived and the latter group died [67]. The use of interferon beta, interferon alpha, and ribavirin was associated with survival rates of 78.3%, 75%, and 68.4%, respectively [66].

Oral lopinavir and ritonavir were used for the treatment of a 64 years old Korean male with confirmed MERS-CoV infection. These medications were started on the fourth day of admission and the patient achieved full recovery after nine days of treatment [63]. One patient was treated with pegylated interferon, ribavirin, and lopinavir/ritonavir and viremia was detected for two days following therapy with triple therapy [64]. In a case series, eight patients received mycophenolate mofetil and all survived [66].

A phase 1 randomized placebo-controlled study utilized a fully human polyclonal IgG antibody (SAB-301) and evaluated the safety and tolerability of this agent in 28 adults compared with 10 adults who received placebo [68]. The trial was registered with ClinicalTrials.gov, number NCT02798188. SAB-301 was well tolerated and the most reported adverse events were headache, elevated creatinine kinase, and albuminuria [68].

### Table 3

A summary of human studies of the use of anti-viral therapy for the treatment of MERS-CoV infection.

| Study type                        | Total # | Supportive therapy | Treatment plan                                                                 | Outcome                                      |
|-----------------------------------|---------|--------------------|--------------------------------------------------------------------------------|----------------------------------------------|
| [60] Retrospective cohort study    | 44 patients | Yes                | SQ PEG-INF α-2a + PO Ribavirin for 8–10 days:                                  | Survival rate after 14 days was 70% versus 29% (P = 0.004) but no change after 28 days (30% versus 17%; P = 0.054) Decreased hemoglobin level as a side effect of ribavirin |
| Treatment group (n = 20) versus control group (n = 24) |         |                    | INF-α-2a + PO Ribavirin                                                                 |                                              |
| [58] Retrospective observational studies | Two patients | Yes                | 1st patient: SQ PEG-INF α-2b + PO Ribavirin                                    | There was a drop in hemoglobin level The patient improved and discharge home After 14 days the patient recovered from MERS-CoV Died after two months as a result of MDR and hospital-acquired infections |
| |         |                    | 2nd patient: SQ PEG-INF α-2b 1 for 3 days + Ribavirin PO                  |                                              |                                              |
| [59] Retrospective observational studies | 5 patients | Yes                | Ribavirin for 5 days + SQ INF α-2b                                            | Died from multi-organ failure Drop in platelet Died from multi-organ failure Patient developed pancreatitis Died from multi-organ failure hemoglobin dropped and bilirubin increased and dialysis was required Died from multi-organ failure Increased lipase Died from multi-organ failure Increased lipase |
| |         |                    | Ribavirin for 5 days + SQ INF α-2b for 2 doses.                          |                                              |                                              |
| |         |                    | Ribavirin PO for 5 days + SQ INF α-2b.                                   |                                              |                                              |
| |         |                    | Ribavirin PO for 5 days + SQ INF α-2b for 2 doses.                       |                                              |                                              |
| |         |                    | Ribavirin PO for 5 days + SQ INF α-2b for 2 doses.                       |                                              |                                              |
| [63] Case report                  | 1 patient | No                 | Lopinavir/Ritonavir PO + Ribavirin PO + PEG-INF α-2a SQ                      | Improved No fever after 2 days Discharge after 9 days Developed hemolytic anemia, electrolyte disturbance, and kidney and liver dysfunction. The fatality rate was 85% in INF-α-2a vs 64% in INF-β-1a. Complete recovery and discharge home. |
| [62] Retrospective Cohort Study    | 24 patients | Yes                | 1st grp: 13 pts INF-α-2a SQ + PO Ribavirin                                     | The fatality rate was 85% in INF-α-2a vs 64% in INF-β-1a. Complete recovery and discharge home. |
| [65] Case series                  | 2 patients | Yes                | 1st patient as treatment and 2nd patient as prophylaxis                       |                                              |
| |         |                    | SQ PEG-INF α-2b:                                                      |                                              |
| [71] case series                  | 11 patients |                    | Ribavirin PO                                                                  |                                                |
| [70] Randomized control trial     | The enrollment began in Nov. 2016                                     |                    | 100 mg Lopinavir/100 mg Ritonavir PO q12 h for 14 days + INF-β1b 0.25 mg/ml SQ on alternative days for 14 days. | Survival of all patients Result is not yet published |
| [66] Case series                  | 23 patients |                    | Interferon beta                                                              | 18/23 (78.3)                                |
| [66] Case series                  | 8 patients  |                    | Interferon alpha                                                             | 6/8 (75)                                    |
| [66] Case series                  | 19 patients |                    | Ribavirin                                                                    | 13/19 (68.4)                                |
| [66] Case series                  | 8 patients  |                    | Mycophenolate mofetil                                                        | 8/8 (100)                                   |
| [72] case report                  | 1 patient  |                    | ribavirin and interferon-alfa 2a                                             | Died                                        |
| [67] case series                  | 6 patients  |                    | ribavirin and interferon-alfa 2b                                            | 3/6 (50)                                    |

*PEG-INF: pegylated interferon; gp: group.*
Community case clusters of Middle East respiratory syndrome coronavirus in hafz Al-batin, kingdom of Saudi Arabia: a descriptive genomic study. Int J Infect Dis 2014;24:63-8. https://doi.org/10.1016/j.ijid.2014.03.1372.

[7] Drosten C, Murthi D, Corman VM, Hussain R, Al Maati M, HajDumar W, et al. An observational, laboratory-based evaluation of the clinical spectrum of Middle East respiratory syndrome coronavirus (MERS-CoV) in Jeddah and Riyadh, kingdom of Saudi Arabia. Clin Infect Dis 2014;60:69-77. https://doi.org/10.1093/cid/ciu82. 2015.

[8] Memish ZA, Al-Thawfiq JF, Alhakeem RF, Ansari A, Alharby KD, Almahallawi MS, et al. (MERS-CoV) a cluster analysis with implications for global management of suspected cases. Trav Med Infect Dis 2015;13:311-4. https://doi.org/10.1016/j.tmaid.2015.06.012.

[9] El Boushi HH, Abdalla MN, Al Arbash H, Al Athayz Z, Al Sal S, Latif ZA, et al. An outbreak of Middle East respiratory syndrome (MERS) due to coronavirus in Al-Abasa region, Saudi Arabia. East Mediterr Health J 2015;21:468-75. 2016.

[10] Balkhy HH, Alzahrani TH, Alshammari MM, Baffoe-Bonnie H, Al-Abdely HM, El-Saedi A, et al. Notes from the field: nosocomial outbreak of Middle East respiratory syndrome coronavirus in a tertiary care hospital-Riyadh, Saudi Arabia. MMWR Morb Mortal Wkly Rep 2015;65:163-4. https://doi.org/10.15585/mmwr.mm6506a5. 2016.

[11] Balkhy HH, Alzahrani TH, Alshammari MM, Baffoe-Bonnie H, Al Arbash H, Hijazi R, et al. Description of a hospital outbreak of Middle East respiratory syndrome in a large tertiary care hospital in Saudi Arabia. Infect Control Hosp Epidemiol 2016;37:1147-55. https://doi.org/10.1017/ice.2016.132.

[12] Assiri AM, Bin Saeed AA, Al Rabeeah AA, Cummings DAT, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus: An observational, laboratory-based study of outbreaks of middle East respiratory syndrome coronavirus in Saudi Arabia linked to hospital outbreak with continued circulation of recombinant virus. Open Forum Infect Dis 2016;3:ofo165. https://doi.org/10.1093/ofid/ofo165. July 1-August 31, 2015.

[13] Nazer RI. Outbreak of Middle East respiratory syndrome coronavirus causes high fatality after cardiac operations. Ann Thorac Surg 2017;104:e127-9. doi:https://doi.org/10.1016/j.athoracsur.2017.02.072.

[14] Assiri A, Abdeli GR, Bin Saeed AA, Alshukairi A, Al-Masry M, Choudhry AJ, et al. Multifacility outbreak of Middle East respiratory syndrome in Taif, Saudi Arabia. Emerg Infect Dis 2016;22:32-40. https://doi.org/10.3201/eid2201.151370.

[15] Hunter JC, Nguyen D, Aden B, Al Bandar Z, Al Dhuberi W, Abu Elkheir K, et al. Transmission of Middle East respiratory syndrome coronavirus infection in intensive healthcare settings, Abu dhabi. Emerg Infect Dis 2016;22:647-56. https://doi.org/10.3201/eid2204.151615.

[16] Cauchemez S, Van Kerkhove MD, Riley S, Donnelly CA, Fraser C, Ferguson NM. Transmission scenarios for middle east respiratory syndrome coronavirus (MERS-CoV) and how to tell them apart. 18. pii; 2013. p. 20503.

[17] Cauchemez S, Fraser C, Van Kerkhove MD, Donnelly CA, Riley S, Rambaut A, et al. Middle East respiratory syndrome coronavirus: quantification of the extent of the epidemic, surveillance biases, and transmissibility. Lancet Infect Dis 2014;14:50-6. https://doi.org/10.1016/S1473-3099(13)70304-9.

[18] Assiri A, McGaer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DAT, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med 2013;369:407-16. https://doi.org/10.1056/NEJMoa1306742.

[19] Chowell G, Abdirizak F, Lee S, Lee J, Jung E, Nishiura H, et al. Transmission characteristics of MERS and SARS in the healthcare setting: a comparative study. BMC Med 2015;13:214. doi:https://doi.org/10.1186/s12916-015-0450-0.

[20] Al-Abdallat MM, Payne DC, Alsaghari S, Rha B, Tohme RA, Abdeli GR, et al. Hospital-associated outbreak of Middle East respiratory syndrome coronavirus: a serologic, epidemiologic, and clinical description. Clin Infect Dis 2014;59:1225-33. https://doi.org/10.1093/cid/ciu359.

[21] Hijawi B, Abdallat M, Sayyadah Y, Alsaghari S, Haddadin A, Jaarour N, et al. Novel coronavirus infections in Jordan, April 2012: epidemiological findings from a retrospective investigation. East Mediterr Health J 2013;19:Suppl 1:S12-8.

[22] Chowdhury IK, Tomczyk SM, Almazroui AH, Al-Awadi AM, Banjar AA, Al-Mughr H, Aloranski MM. MERS-CoV outbreak in Jeddah—a link to health care facilities. N Engl J Med 2014;372:846-54. https://doi.org/10.1056/NEJMoa1408636. 2015.

[23] Al Rubadi B, Bawareh N, Omar H, Alsalmi H, Alshukairi A, Qushmaq I, et al. Patient characteristics infected with Middle East respiratory syndrome coronavirus infection in a tertiary hospital. Ann Thorac Med 2016;11:28-31. https://doi.org/10.4103/1817-1737.180027.

[24] Fagbo SF, Skakni L, Chu DKW, Garbati MA, Joseph M, Peiris M, et al. Molecular epidemiology of hospital outbreak of Middle East respiratory syndrome, Riyadh, Saudi Arabia. 2015 Emerg Infect Dis 2014;21. doi:https://doi.org/10.3201/eid2111.150944. 1981-8.

[25] Almekhlafi GA, Albarakk MM, Mundeerah Y, Hassan S, Alwan A, Abudayah A, et al. Presentation and outcome of Middle East respiratory syndrome coronavirus in saudi intensive care unit patients. Crit Care 2016;20:123. https://doi.org/10.1186/s13054-016-1903-8.

[26] Saad M, Omrani AS, Baig K, Rahhal A, Elnine F, Matin MA, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. Int J Infect Dis 2014;29:201-6. https://doi.org/10.1016/j.ijid.2014.09.003.

[27] Mohar D, Liberati A, Tetzlafer-Bonnie H, Al-Abdely HM, El-Saed GA, Albarrak MM, Mandourah Y, Hassan S, Alwan A, Abudayah A, et al. Cluster of Middle East respiratory syndrome coronavirus infections related to a likely unrecognized asymptomatic or mild case. Int J Infect Dis 2015;37:1668-72. https://doi.org/10.1016/j.ijid.2015.07.001.

[28] Memish ZA, Zamaal AI, Al-Hakeem RF, Al-Rehabez A, a, Stephens GM. Family cluster of Middle East respiratory syndrome coronavirus infections. N Engl J Med 2015;372:2467-94. https://doi.org/10.1056/NEJMoa1503729.

[29] Memish ZA, Cotten M, Watson SJ, Kellam P, Zamaal A, Al Hakeem RF, et al. Al.
and is strongly inhibited by cyclosporin A or interferon-α treatment. J Gen Virol 2013;94:1749–60. https://doi.org/10.1099/vir.0.052910-0. 30

[30] Falzarano D, de Wit E, Martelaro C, Callison J, Munster VJ, Feldmann H. Inhibition of novel β coronavirus replication by a combination of interferon-αb2 and ribavirin. Sci Rep 2016;6:22208. https://doi.org/10.1038/srep22208.

[31] Chan JF, Chan KH, Kao RY, To KK, Zheng BJ, Li CP, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Infect 2013;67:606–16. https://doi.org/10.1016/j.jinf.2013.09.029.

[32] Wu CY, Jan JT, Ma SH, Kuo CJ, Jhan HF, Cheng SY, et al. Small molecules targeting severe acute respiratory syndrome coronavirus. Proc Natl Acad Sci United States Am 2004;101:10012–7. https://doi.org/10.1073/pnas.0403596101.

[33] de Wilde AJ, Jochnich D, Posthumus CC, Zevenhoven-Dobbe JC, van Neuenhuizen S, Bestebroer TM, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother 2014;58:4875–84.

[34] Shirato K, Kawaue M, Matsuura M. Middle East respiratory syndrome coronavirus (MERS-CoV) infection mediated by the Transmembrane serine protease TMPRSS2. J Virol 2013;87:12552–61. https://doi.org/10.1128/JVI.01890-13.

[35] Li X, Liao Q, Zuo Y, Zhao K, Li Y, et al. Unexpected discovery of Middle East respiratory syndrome coronavirus fusion inhibitor. Nat Commun 2014;5:3067. https://doi.org/10.1038/ncomms4067.

[36] Shirato K, Kawaue M, Matsuura M. Middle East respiratory syndrome coronavirus infection mediated by the Transmembrane serine protease TMPRSS2. J Virol 2013;87:12552–61. https://doi.org/10.1128/JVI.01890-13.

[37] Nitazoxanide Rossignol J-F. A new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. J Infect Public Health 2016;9:227–30. https://doi.org/10.1016/j.jiph.2016.02.001.

[38] Zhou N, Pan T, Zhang J, Li Q, Zhang X, Bai C, et al. Glycopeptidyl Antibiotics potently inhibit Cathepsin L in the late Endosome/Lysosome and block the entry of Ebovirus, Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus (SARS-CoV). J Virol 2016;90:9294–32. https://doi.org/10.1128/JVI.01610-16.

[39] Tai W, Zhao G, Sun S, Guo W, Yang Y, Tao X, et al. A recombinant receptor-binding domain of MERS-CoV in trimeric form protects human dipепtide peptidase 4 (DPP4) transgenic mice from MERS-CoV infection. Virology 2014;469:375–82. https://doi.org/10.1016/j.virol.2014.06.005.

[40] de Wilde AJ, Zevenhoven-Dobbe JC, van der Meer Y, Bestebroer TM, Dijkman P, van der Meden F, et al. Treatment with interferon-β 1b (MIRACLE trial): study protocol for a randomized, open-label, pragmatic, parallel-group, phase 3, non-inferiority trial of an interferon treatment option for patients with severe Middle Eastern respiratory syndrome coronavirus pneumonia: a prospective study. Int J Infect Dis 2014;20:42–6. https://doi.org/10.1016/j.ijid.2013.12.003.

[41] Omran A, Saad MM, Baig K, Babulow A, Abdul-Matin M, Al-Arbaeen AA, et al. Ribavirin and interferon alfa-2a for Middle East respiratory syndrome coronavirus pneumonia: a retrospective cohort study. Lancet Infect Dis 2014;14:1940–5. https://doi.org/10.1016/S1473-3099(14)70209-X.

[42] Momattin H, Mohammed K, Zuma A, Momattin H, Al-Tawab S, Al-Jazairy R, et al. Therapeutic options for Middle East respiratory syndrome coronavirus (MERS-CoV): lessons from a systematic review of SARS-CoV therapy. Int J Antimicrob Agents 2017;13:779–82. https://doi.org/10.1016/j.ijantimicag.2017.07.002.

[43] Shahbod-Noori A, Al-Jeffri A, Simhairi R, Shamma O, Siddiqui N, et al. IFN-α2a or IFN-αb1a in combination with favipiravir to treat MERS-CoV infection. J Infect Dis 2018;217:1085–9. https://doi.org/10.1093/infdis/jiy025.

[44] Yi J, Wu J, Ee K-J, Joo S-J, Jung H-C. Combination therapy with lipovinpiravir, ribavirin, and interferon-alpha for Middle Eastern respiratory syndrome coronavirus (MERS-CoV) infection: a case report. Antivir Ther 2015. https://doi.org/10.3851/IMP3002.

[45] Spanakis N, Tsiodras S, Haagmans BL, Raj VS, Pontikis K, Koutsoukou A, et al. Virological and serological analysis of a recent Middle East respiratory syndrome coronavirus infection case on a triple combination antiretroviral reg. J Antimicrob Agents 2014;44:528–32. https://doi.org/10.1093/acerbhb/htv131.

[46] Al-Khalidi M, Al Rabiah F, Khan B, Al Moberieek A, Butt TS, Al Mutayer E. Ribavirin and interferon-α2b as primary and preventive treatment for Middle East respiratory syndrome coronavirus pneumonia: a preliminary report of two cases. Antivir Ther 2015;20:87–91. https://doi.org/10.3851/IMP2792.

[47] Al-Khalidi M, Al-Ghamdi M, Alghamdi KM, Ghandoora Y, Alzahrani A, Salah F, Alsulami A, et al. Treatment outcomes for patients with middle eastern respiratory syndrome coronavirus (MERS-CoV) infection at a coronavirus referral center in the kingdom of Saudi Arabia. BMC Infect Dis 2016;16:174. https://doi.org/10.1186/s12879-016-1492-y.

[48] Khaliq K, Khan B, Al Rabiah F, Alismaili R, Saleemi S, Rehman-Khalig AM, et al. Middle Eastern respiratory syndrome coronavirus (MERS-CoV): case reports from a tertiary care hospital in Saudi Arabia. Ann Saudi Med 2014;34:396–400. https://doi.org/10.1016/j.jsl.2014.07.001.

[49] Beigel JH, Voel J, Kumar P, Raviglione K, Wu H, Jiao J-A, et al. Safety and tolerability of a novel, polyclonal human anti-MERS coronavirus antibody produced from transchromatographic bovine plasma in humans with severe Middle Eastern respiratory syndrome coronavirus pneumonia and ARDS. Respir Care 2016;61:340–8. https://doi.org/10.4187/respcare.03526.

[50] Malik A, El Masry KM, Ravi M, Sayed F. Middle East respiratory syndrome corona virus (MERS-CoV) infection mediated by the Transmembrane serine protease TMPRSS2. J Virol 2013;87:61. https://doi.org/10.1128/JVI.01890-13.

[51] Arabi YM, Alothman A, Balkhy HH, Al-Dawood A, Al-Johani S, Al Harbi S, et al. Severe Middle Eastern respiratory syndrome (MERS) in Saudi Arabia: an observational study. Int J Infect Dis 2014;20:40–6. https://doi.org/10.3851/IMP3002.

[52] Malik A, El Masry KM, Ravi M, Sayed F. Middle East respiratory syndrome coronavirus pneumonia and ARDS. Respir Care 2016;61:340–8. https://doi.org/10.4187/respcare.03526.

[53] Al-Tawab S, Al-Mubareeke A, Butt TS, Al Mutayer E. Ribavirin and interferon-α2b as primary and preventive treatment for Middle East respiratory syndrome coronavirus pneumonia: a preliminary report of two cases. Antivir Ther 2015;20:87–91. https://doi.org/10.3851/IMP2792.

[54] Al-Khalidi M, Al-Ghamdi M, Alghamdi KM, Ghandoora Y, Alzahrani A, Salah F, Alsulami A, et al. Treatment outcomes for patients with middle eastern respiratory syndrome coronavirus (MERS-CoV) infection at a coronavirus referral center in the kingdom of Saudi Arabia. BMC Infect Dis 2016;16:174. https://doi.org/10.1186/s12879-016-1492-y.

[55] Beigel JH, Voel J, Kumar P, Raviglione K, Wu H, Jiao J-A, et al. Safety and tolerability of a novel, polyclonal human anti-MERS coronavirus antibody produced from transchromatographic bovine plasma in humans with severe Middle Eastern respiratory syndrome coronavirus pneumonia and ARDS. Respir Care 2016;61:340–8. https://doi.org/10.4187/respcare.03526.