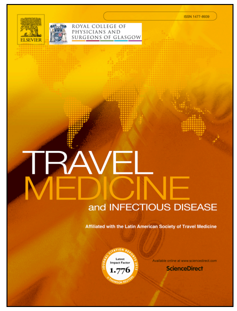

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A Systematic Review of Therapeutic Agents for the Treatment of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

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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 few promising therapeutic agents in 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.

Introduction:

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was first identified in 2012 and since then the disease attracted an increased 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 had 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 had 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.

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 Coronaviruses 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.

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 (Figure 1).

In Vitro Studies:

There were many i*n 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-a2b [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- alfa 2b (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 mesylate 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 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 (ID_{50}) 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].

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 one hour prior to infection with MERS-CoV. After 48 hours, 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 13.58 μM with high 50% cytotoxicity concentration (CC_{50}) 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].

Chloroquine, Chloropromazine, and loperamide were tested on Huh7 cells [43]. The cells were treated 1-hour prior to infection. Antiviral activity of chloroquine was dose-dependent. Chlorpomazine showed activity against MERS-CoV with EC50 of 4.9 ± 1.2 μM and CC50 of 21.3 ± 1.0 μM. Loperamide, an antidiarrheal drug, inhibited MERS-CoV and induced CPE. Two kinase signaling (ABL1) 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 hours 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 hours, 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 pro-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 hours 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 triflupromazine 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].

Animal Studies:

Monoclonal antibodies against MERS-CoV had been tested in animal models of MERS-CoV infection. 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 diffrence 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 eight hours 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 chemotactic 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 hours after inoculation; Lopinavir with Ritonavir at 6, 30, and 54 hours after inoculation; or Interferon- Beta-1b subcutaneous at 8- and 56-hours 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 in untreated, and Mycophenolate treated groups (67%) than Lopinavir/Ritonavir treated and Interferon-Beta-1 b treated groups (0-33%) after 36 hours of inoculation [52].

The human dipeptyl peptidase-4 (hDPP4) is a receptor for cell binding and entry of MERS-CoV. A transgenic mouse model with hDPP4 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 hDPP4 in mouse lungs (Ad5-hDPP4-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 six hours 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 hDPP-4 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 MESR-CoV. The treatment group had a 100% survival rate compared with 0% survival rate in the control group [56].

The impact of a trans-chromosomic (Tc) bovine, fully human polyclonal immunoglobulin G (IgG) antibodies were tested on Ad5-hDPP4-transduced mice five days after transduction and 12 hours 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 hDPP4 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].

Human Studies:

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 PEG-INF- 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 NCT02788188. SAB-301 was well tolerated and the most reported adverse events were headache, elevated creatinine kinase, and albuminuria [68].

Discussion:

Since the emergence of MERS-CoV infection there was a large interest in the development of an effective therapy for this disease. In this review, we summarized the available literature on possible therapeutic options including *in vitro,* animal and human studies. In vitro studies showed superiority of IFN-β compared to IFN-α2b, IFN-γ, IFN-universal type 1 and IFN-α2a

[28] and PEG-IFN-α had excellent CPE inhibition [29]. Moreover, the combination of INF-α2b and ribavirin in Vero cells showed augmentation of action and facilitates the reduction of the doses of IFN-α2b and ribavirin to lower concentrations suggesting possible utility in clinical use [30]. Saracatinib with Gemcitabine had no difference in cytotoxicity compared with Saracatinib alone but was less cytotoxic compared with gemcitabine alone [44]. There were many drugs that were used in vitro and showed effectiveness, however, translating the findings from these studies into clinical trial remains of particular importance especially taking into consideration availability, pharmacokinetic properties, pharmacodynamic characteristics and possible side effects [69].

Avaialble clincial experience regarding the therapy for MERS-CoV relies on limited case reports and observational case-series. The most widely used combination is ribavirin and IFN and experience comes from limited case reports and a number of observational studies. These studies are non-homogeneous in nature and thus a common conclusion could not be obtained to make firm recommendations for the use of this combination in routine clinical practice outside of prospective clinical studies [69].

The combination of lopinavir/ritonavir and interferon- beta- 1b was used in common marmosets [52] and was used in two patients with good outcome [63–65]. This combination is being considered in a randomized control trial in Saudi Arabia. The enrollment for the study began in November 2016 and the results are not available yet [70]. The study was registered on 27 July 2016 at ClinicalTrials.gov, with an ID: NCT02845843. And this is the only currently ongoing clinical therapeutic trial for MERS-CoV therapy.

In 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. Thus, any such therapy should be used in conjunction with clinical trials. An interesting strategy is repurposing old drugs against MERS-CoV and this deserves further consideration and use in clinical setting

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Figure 1: A flow diagram of the search strategy according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]

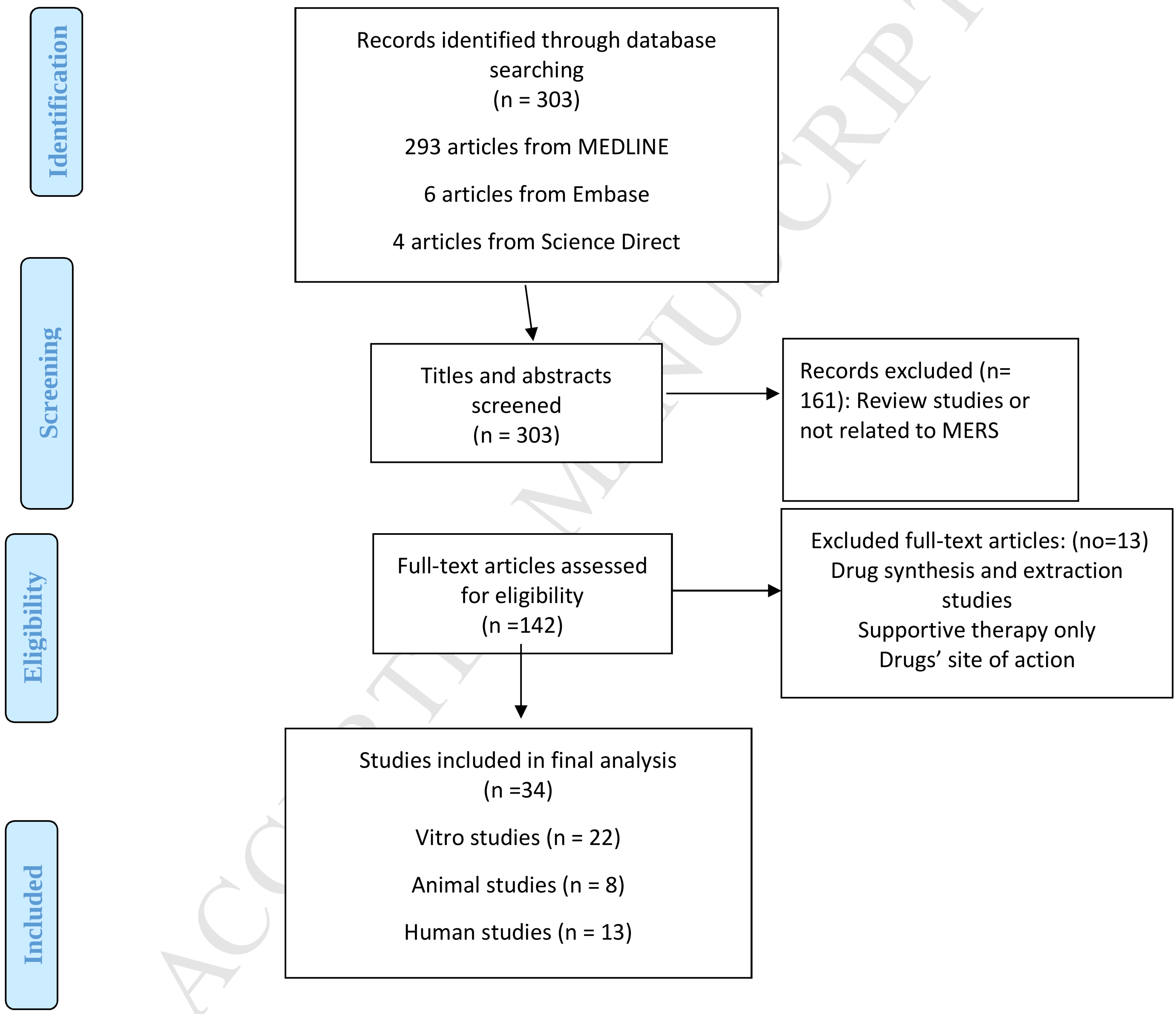

Table 1: A summary of *in Vitro* Studies evaluating medications against MERS-CoV

	Study type	Cell Type	Treatment	Outcome
[29]	In vitro Comparator study	MERS-CoV infected Vero cells and mock-infected Huh7 cells.	Cyclosporin 3 µg DMSO (a solvent control Control)	No change in CPE
			Cyclosporin 9 µg DMSO (a solvent control Control)	CPE inhibited and no change on the cell viability on the infected Vero cells compared with mock-infected cells
		MERS-CoV infected Huh7 cells and mock-infected Huh7 cells.	Cyclosporin 3.75 µg, 7.5 µg, and 15 µg	CPE reduced or inhibited by 7.5 µg and 15 µg Cyclosporine.
		MERS-CoV infected Vero cells	PEG-INF-α2b at t= -4h, t= 0h, or t= 4h of	CPE reduced at 1 ng/ml and complete inhibition at doses 3, 10, 30, 100, 300, or 1000 ng/ml.

			infection at doses range from 0 ng/ml to 1000 ng/ml	
[30]	In vitro Comparator study	hCoV-EMC infected Vero cells	INF-α2b	IC_{50} = 58.08 U/ml, IC_{90} =320.11 U/ml, and IC_{99}= 2061.89 U/ml CPE reduced at 250 U/ml and complete inhibition at ≥ 1000 U/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.
			Ribavirin	IC_{50} = 41.45 μg/ml, IC_{90} = 92.15 μg/ml, and IC_{99} =220.40 μg/ml CPE reduced at 100 μg/ml and complete inhibition at ≥ 200 μg/ml. Genome copies reduced by 0.82-log at 500 μg/ml and highest reduction by 2.04-log at 2000 μg/ml. Viral titer reduced by 1.24-log at 100 μg/ml and highest reduction by 4.05-log at 2000 μg/ml.

			INF-α2b + Ribavirin	CPE reduced at 12 µg/ml Ribavirin and 62 U/ml INF-α2b and complete inhibition at 25 µg/ml Ribavirin and 125 U/ml INF-α2b Ribavirin + INF-α2b at 1:5, Viral titer reduced by 0.4 to 2.16-log compared with INF-α2b alone.
		LLC-MK 2 infected cells	INF-α2b	IC_{50} = 13.26 U/ml, IC_{90} = 44.24 U/ml, and IC_{99} =164.73 U/ml. Reduced viral protein level with increased dose starting at 250 U/ml. Viral titer reduced by 3.97-log at 2000 U/ml
			Ribavirin	IC_{50} = 16.33 µ/ml, IC_{90} = 21.15 µg/ml, and IC_{99} = 28.02 µg/ml. Reduced viral protein level with dose 50 µg/ml (Not dose dependent) Viral titer reduced below the detection threshold of 13.7 $TICD_{50}$/ml at 200 µg/ml
			INF-α2b + Ribavirin	Reduced viral protein level with dose INF-α2b 250U/ml and Ribavirin at 50 µg/ml.

[41]	In vitro Comparator study	Vero cells	Toremifene	EC_{50} = 12.9 μM with no virus reduction
			Chlorpromazine	EC_{50} = 9.5 μM with no cytotoxicity Virus reduction by 3.1 log_{10} if dose >15μM
			Chloroquine	No virus reduction
		MDMs	Toremifene	Dose treated too low to determine EC_{50} with high cytotoxicity. Virus reduction by 1-1.5 log_{10} if dose >20μM with increased in the toxicity.
			Chlorpromazine	EC_{50} = 13.58 μM with high cytotoxicity CC_{50} = 25.64 μM, SI was 1.9 Virus reduction by 2 log_{10} with narrow therapeutic window and high toxicity
			Chloroquine	No antiviral activity and no cytotoxicity.
		MDDCs	Toremifene	Virus reduction by 1-1.5 log_{10} if dose >20μM with increased in the toxicity.
			Chlorpromazine	Virus reduction by 2 log_{10} with narrow therapeutic window and

				high toxicity
			Chloroquine	No antiviral activity and no cytotoxicity
[33]	In vitro Comparator study	Huh7 cells	Chloroquine Chlorpromazine Loperamide Lopinavir Pre-infection	Chloroquine: dose-dependent, EC_{50} = 3.0 ±1.1 μM and CC_{50} = 58.1 ±1.1 μM, SI was 19.4 Chlorpromazine: Complete inhibition at 12 μM, EC_{50} = 4.9 ±1.2 μM and CC_{50} = 21.3 ±1.0 μM, SI was 4.3 Loperamide: Complete inhibition at 8 μM, EC_{50} = 4.8 ±1.5 μM and CC_{50} = 15.5 ±1.0 μM, SI was 3.2 Lopinavir: Complete inhibition at 12 μM, EC_{50} = 8 ±1.5 μM and CC_{50} = 24.4 ±1.0 μM, SI was 3.1
[43]	In vitro Comparator study	Vero E6 MRC5	Imatinib in the first 4hrs of infection versus 5 hrs post infection	Iamtinib at time of infection is dose dependent. Viral level higher at post-infection compared to before infection ($P < 0.05$) Genomic RNA inhibited if drug added before infection ($P < 0.05$) but no effect if added post-infection

				CCF2 cleavage reduced by 80% (P< 0.001)
[49]	In vitro Comparator study	Pooled Plasma inoculated with MERS-CoV	Amotosalen and Ultraviolet A light	Viral titer reduced by 4.67 ± 0.25 log pfu/ml with no detection of the viable viruses. Viral genomic titer by RT-qPCR: no viral RNA had been detected on the treated cells
[44]	In vitro Comparator study	Huh-7 cells infected with MERS-CoV	Saracatinib	MERS-CoV infected cells: EC_{50} = 2.9 µM and CC_{50} > 50 µM, SI >17, Dose 1 µM: viral titer reduced by > 50% (P<0.05) with no effect on viral N protein after 24 hrs Dose 10 µM: reduced by 90% (P<0.05) with complete depletion on the viral N protein after 24 hrs. Complete inhibition of viral genomic RNA and mRNA synthesis (P<0.0001) Viral titer: Pretreatment: no difference At time of infection: marked reduction with significant a decrease

				of viral genomic RNA and mRNA synthesis. Post treatment (within 2 hrs.): complete inhibition (P< 0.0001) Post treatment (after 4hrs): less effect (P<0.05)
		Huh-7 cells infected with rMERS-Cov.	Saracatinib	rMERS-CoV infected cells: EC_{50} = 9.3 μM
		Huh-7 cells infected with rMERS-Cov-S2.	Saracatinib	rMERS-CoV-S2 infected cells: EC_{50} = 9.0 μM
		Huh-7 cells infected with MERS-CoV	Gemcitabine	EC_{50} = 1.2 μM with complete viral depletion at dose ≥ 1 μM
			Saracatinib + Gemcitabine	Synergistic effect at combination index of 0.529 Cytotoxicity: no difference compared with Saracatinib and less compared with Gemcitabine
[45]	In vitro Comparator study	Vero E6	Resveratrol	Reduced cell death at 125-250 μM (MTS assay P<0.05, neutral red uptake assay P< 0.005) Less cytotoxicity even at higher concentration. Viral RNA level: At concentration 31.25-250 μM: after 48hr lower than after 24 hrs

				After 48 hr at concentration 150µM: lower ($P<0.05$), at concentration 200µM ($P<0.01$), at concentration 250µM ($P<0.001$). If the drug added at time of infection: no difference in the cell proliferations and viral titers. After 24hr, the inhibition of N protein is dose dependent manner. At concentration 150µM: limited decrease in the N protein At concentration 250µM: elimination of N protein. Inhibited Caspase 3 cleavage: dose dependent manner. If drug administered consecutively at lower dose: Ever 24 hrs, 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 ($P < 0.001$)
[46]	In vitro Comparator study	HAE infected with MERS-CoV	GS-441524 or Remdesivir (GS-5734)	GS-44152: EC_{50} = 0.86 µM Remdesivir: EC_{50} = 0.074 µM

				More reduction in viral titer if the drug were added 24-72 hrs. post infection.
[47]	In vitro Comparator study	HAE infected with MERS-CoV	K22	Significant reduction in the viral replication and dsRNA level.
[48]	In vitro Comparator study	MERS-CoV infected cells	Novel peptide (P9)	IC_{50} = 5 μg/ml >95% reduction at concentration > 25 μg/ml
[36]	In vitro Comparator study	Vero-TMPRSS2 infected cells	Camostat	At dose 10 μM, decreased viral entry by 15-fold
		Vero-TMPRSS2-negative infected cells	Camostat	At dose 10 μM, no effect on the viral entry
		Calu-3 cells	Camostat	At dose 10 μM, decreased viral entry by 10-fold Viral RNA suppressed by 90-fold Cell death delayed by 2 days post infection At dose 100 μM, Viral RNA suppressed by 270 folds 3 days post

				infection Cell death delayed by 5 days post infection
		MRC-5 cells or WI-38 cells	Camostat	No effect on the viral RNA at 3 days post infection. At dose 10 μM, there was no effect on the cell death At dose 100 μM, the cell death partially suppressed.
		Vero-TMPRSS2 infected cells	EST (an inhibitor of endosomal cathepsins)	At dose 10 μM, slight inhibition of viral entry
		Vero-TMPRSS2-negative infected cells	EST (an inhibitor of endosomal cathepsins)	At dose 10 μM, inhibit viral entry
		Calu-3 cells	EST (an inhibitor of endosomal cathepsins)	At dose 10 μM, slight inhibition of viral entry
		Vero-TMPRSS2 infected cells	Camostat + EST (an inhibitor of endosomal cathepsins)	Decreased viral entry by 180-fold
		Calu-3 cells MRC-5 cells	Camostat + EST+ Leupeptin	No significant difference in the viral entry

		WI-38 cells	Single treatment + Leupeptin	
		Vero-TMPRSS2-negative infected cells	Cathepsin L inhibitor Cathepsin K inhibitor	Inhibit the viral entry by 40-fold
		Vero-TMPRSS2-negative infected cells	Cathepsin B inhibitor Cathepsin S inhibitor	No effect on the viral entry
		Calu-3 cells	Leupeptin	Dose dependent effect Blocked viral entry at 10-100 μM
		MRC-5 cells	Leupeptin	No effect on the viral entry
		WI-38 cells	Leupeptin	No effect on the viral entry
[42]	In vitro Comparator study	Vero E6 cells infected with MERS-CoV	Chlorpromazine	EC_{50} = 9.51 μM with low toxicity
			Triflupromazine	EC_{50} = 5.76 μM with low toxicity
			Imatinib	EC_{50} = 14.69 μM with low toxicity

			Dasatinib	EC_{50} = 5.47 μM with low toxicity
			Nilotinib	No significant inhibition of MERS-CoV
			Gemciatbine	EC_{50} = 1.22 μM with low toxicity
			Toremifene	EC_{50} = 12.92 μM with low toxicity

* CPE: cytopathic effect; PEG-INF: pegylated interferon; INF: interferon; IC_{50}: inhibitory concentration of 50% of cells, IC_{90}: inhibitory concentration of 90% of cells; IC_{99}: inhibitory concentration of 99% of cells; EC_{50} and $EC_{90:}$ 50% and 90% maximal effective concentration; CC_{50}: cytotoxicity concentration that kills 50% of cells; RT-qPCR: Real time Quantitative polymerase chain reaction;

Table 2: 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
[50]	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
[53]	Comparator trial	hDPP4-Tg mice	No	After 1 day of inoculation IV hMS-1 2mg/kg versus Trastuzumab (Treatment)	hMS-1 vs Tractuzumab: • Less viral titer Less lung injury • Fewer histopathological changes • Less decrease in the body weight

					• More survival rate
[54]	Comparator trial	Ad5-hCD26-transduced mice	No	Either 1d before or 1 d after inoculation IV mAb 4C2h (Prophylaxis and treatment) or no treatment	Decreased Viral titer
[51]	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.
[55]	Comparator trial	Ad5-hCD26-transduced mice	No	Treatment group: Intranasal peptide HR2P-M2 200mcg 6h before inoculation (Prophylaxis) Control group (no treatment)	Decreased viral titer
				1st gp: 200 mcg intranasal HR2P-M2 2nd gp: 2000 U intranasal INF-β 3rd gp: Combination 4th gp: no treatment 6h before inoculation (prophylaxis)	Decreased viral titer in all treated group compared with the control group with complete clearance in mice which received combination treatment.
				1st gp: 200 mcg intranasal HR2P-M2 2nd gp: 2000 U intranasal INF-β 3rd gp: Combination	Viral inhibition in all treated group with the greatest reduction in the combination group. greater reduction in viral titer in

				4th gp: no treatment 12 and 36 h after inoculation (treatment)	the 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
[56]	Comparator trial	hDPP-4 Tg mice	No	1st gp: NbMS10-Fc single dose 2nd gp: Trastuzumab Before inoculation (prophylaxis)	Better survival rate Steady weight compared with sharply decreased in the weight on the control group
				1st gp: NbMS10-Fc single dose 2nd gp: Trastuzumab 3d after inoculation (treatment)	Better survival rate Less weight loss
[52]	Comparator trial	12 healthy common	No	1st gp: no treatment 2nd gp: Mycophenolate mofetil	Lopinavir/Ritonavir and INF- β-1b have a better clinical score, less weight

		Marmosets		intraperitoneal after 8hr of inoculation 3rd gp: + Ritonavir PO at 6, 30, and 54 hrs after inoculation, 4th gp: INF- β-1b SQ at 8 and 56 hrs post inoculation. (Treatment)	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
[57]	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 Tc hIgG 500 mcg 3rd gp: no treatment 12 hr before inoculation (prophylaxis)	viral load was lower in SAB-301 vs Tc hIgG group at day 1 The viral titer was lowest in the 500mcg vs Tc hIgG and control

				1st gp: intraperitoneally single dose 500 mcg SAB-301 antibody, 2nd gp: intraperitoneally single dose Tc hIgG 3rd gp: no treatment 1-2 hrs of inoculation (Treatment)	On day 1 and 2 post infection: • Viral titer in SAB-301 antibody group was below the detection level vs control or Tc hIgG •

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

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 Treatment group (n=20) versus control group (n=24)	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

[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
			Yes	2nd patient: SQ PEG-INF α- 2b 1 for 3 days + Ribavirin PO	After 14 days the patient recovered from MERS-CoV. Died after two months as a result of MDR and hospital-acquired infections
[59]	Retrospective observational studies	5 patients	Yes	Ribavirin for 5 days + SQ INF α-2b	Died from multi-organ failure
			Yes	Ribavirin for 5 days + SQ INF α-2b for 2 doses.	Drop in in platelet Died from multi-organ failure

			Yes	Ribavirin PO for 5 days + SQ INF α-2b.	Patient developed pancreatitis Died from multi-organ failure
			Yes	Ribavirin PO for 5 days + SQ INF α-2b for 2 doses.	hemoglobin dropped and bilirubin increased and dialysis was required Died from multi-organ failure
			Yes	Ribavirin PO for 5 days + SQ INF α-2b for 2 doses.	Increased lipase Died from multi-organ failure
[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.
[62]	Retrospective Cohort Study	24 patients	Yes	1st gp: 13 pts INF- α-2a SQ + PO Ribavirin 2nd gp: 11 pt INF-β-1a + PO Ribavirin	The fatality rate was 85% in INF-α-2a vs 64% in INF-β-1a.
[65]	Case series	2 patients	Yes	1st patient as treatment and 2nd patient as prophylaxis SQ PEG-INF- α-2b: Ribavirin PO	Complete recovery and discharge home.
[71]	case series	11		ribavirin and interferon-alfa 2a	Survival of all patients

[70]	Randomized control trial	The enrollment began in Nov. 2016	100mg Lopinavir/100mg Ritonavir PO q12h for 14 days + INF- β1b 0.25mg/ml SQ on alternative days for 14 days.	Result is not yet published
[66]	Case series	23	Interferon beta	18/23 (78.3)
[66]	Case series	8	Interferon alpha	6/8 (75)
[66]	Case series	19	Ribavirin	13/19 (68.4)
[66]	Case series	8	Mycophenolate mofetil	8/8 (100)

[72]	case report	1	ribavirin and interferon-alfa 2a day 12 from onset	died
[67]	case series	6	ribavirin and interferon-alfa 2b	3/6 (50)

* PEG-INF: pegylated interferon; gp: group