The Use of the Available Research Evidence to Crack the Padlock of Sars-CoV-2

Aamir Jalal Al Mosawi

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**ABSTRACT**

It was known earlier that although, SARS-CoV was controlled more than a decade ago, more SARS-like coronaviruses which have been isolated in bats can use the human angiotensin converting enzyme-2 (ACE2) receptor to replicate to high levels in primary human airway, and they had the potential to cause new epidemics. Now, we should remember that it was concluded from earlier experiences that the first and most effective line of defense against a new viral pandemic in the early phases, are antiviral drugs not vaccines developed after rather a lengthy time. The unexpected high mortality associated with the ongoing SARS-CoV-2 in countries like the United States and the United Kingdom confirmed the earlier scientific prediction of the inadequate preparedness of the world to victoriously combat a new virus pandemic. The rational scientific approach to face a potentially fatal viral pandemic with no known effective specific therapies dictate the early use of all the useful preliminary research evidence with prioritizing emphasis on safety to avoid making more harm than good in such situation. We have previously published an evidence-based keys to the therapeutic challenge associated with the emergence of SARS-CoV-2 pandemic. The aim of this paper is to provide and important updates to keys to the therapeutic challenge which are hoped to help in cracking the padlock of SARS-CoV-2.

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**Introduction**

Influenza A virus pandemic (1918-1919) was the most deadly pandemic in modern history of medicine, and was caused by type A/H1N1. Influenza a virus can also cause disease in birds and mammals, and it is the chief circulating widely spread virus in the humans. Thereafter, Influenza viruses allowed another virus to dominate the scene during the 21st century. The 2009 swine-originated virus (pH1N1) pandemic should have informed the scientific of the inadequate preparedness of the world to victoriously combat a new influenza strains pandemic or other new viruses pandemic. Viral pandemics associated with the emergence of new viruses can early defeat the world before vaccine development efforts yield any useful fruit. By now the world should have already declared that the new bat-human corona-virus has been the winner. Waiting for the time when, a vaccine can be used as a main weapon to fight a new viral pandemic is expected to be associated early defeat and too many losses [1, 6].

It was known earlier that although, SARS-CoV was controlled more than a decade ago, more SARS-like coronaviruses which have been isolated in bats can use the human angiotensin converting enzyme-2 (ACE2) receptor to replicate to high levels in primary human airway, and they had the potential to cause new epidemics [1-4]. Now, we should remember that it was concluded from earlier experiences that the first and most effective line of defense against a new viral pandemic in the early phases, are antiviral drugs [1-6].

There are four genera of coronaviruses including alpha-coronaviruses, beta-coronaviruses, gamma-coronaviruses, and delta-coronaviruses. Alpha and beta-coronavirus can infect mammals, while gamma-coronavirus and delta-coronavirus generally infect birds. Four coronaviruses are known to cause mild upper respiratory infection in humans of all ages including infants. The transmission of coronaviruses from animals (birds) to causes respiratory illness has been reported as early as 1969 by Kapikian et al. Community-wide outbreak associated with 229E-like coronavirus has been reported as early as 1970 by Cavallaro and Monto. Until December, 2020, two beta-coronaviruses (SARS coronaviruses and MERS-coronaviruses) were known to cause severe, potentially fatal pneumonia-like illness [1-6].

Errors in the replication of viral genomic RNA of zoonotic coronaviruses led to the emergence of genetically related diverse quasi-species, while the transmission of some of them to a new host species led to the emergence of human severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). SARS-CoV emerged for the first time in Guangdong China in 2002 spread rapidly to many other counties causing more than 8000 cases with about10% mortality. In 2012, it was thought that MERS-CoV was transmitted to humans from bats through an intermediate camel host leading to 1700 cases in 27 countries with about 40% mortality. Increasing number of cases of severe potentially fatal pneumonia caused by a new β-coronavirus was reported from Wuhan China in December 2019, and human-to-human transmission was confirmed early. On the 12th of January, 2020 the

According to the live online update available at https://www.worldometers.info/coronavirus/, on the 17th of June 2020, more than 8.18 million cases have been reported from 188 countries and territories. A total of 443,000 deaths have been resulted, while more than 3.96 million cases have recovered.

On the 26th of March, 2020 the United States has become the country with the world’s third largest population, it surpassed China and Italy as the country with the highest number of confirmed cases in the world.

On the 27th of May 27, 2020, the United States had the most confirmed active cases and deaths in the world, and on the fifth of June, 2020, the United States death rate was 330 per million people, the ninth-highest rate globally.

On the 16th of June, 2020, there have been 298,136 confirmed cases in the United Kingdom and 41,969 of confirmed cases died, and United Kingdom had the world’s second-highest death-rate per capita. More than 90% of the patients died had underlying medical condition or were over 60 years old.

The unexpected high mortality associated with the ongoing SARS-CoV-2 in countries like the United States and the United Kingdom confirmed the earlier scientific prediction of the inadequate preparedness of the world to victoriously combat a new virus pandemic. In Iraq, the spread of SARS-CoV-2 was first recognized during February, 2020 with the report of the first confirmed cases of SARS-CoV-2 infections on the 22nd of February in the province of Najaf. The first reported case in Iraq was an Iranian student of religion. The first case SARS-CoV-2 in the Kurdish region of Iraq in the North of the country was reported on the first of March, 2020. However, the first death from SARS-CoV-2 in Iraq was reported from the province of Sulaymaniyah in the Kurdish region of Iraq. The patient was a 70-year-old man who was known to have chronic heart failure associated with asthmatic manifestations. The second death in death from SARS-CoV-2 in Iraq was reported from the province Baghdad, while the first recovery was reported on the 6th of March. On the 27th of March,2020, all 19 Iraqi provinces have reported confirmed cases, and on the 7th of April, 28,414 tests have been performed with 1202 of them were positive. On the first of April, 2020, the total number of confirmed SARS-CoV-2 cases in Iraq was 728. Early during June, the number of the reported cases exceeded 12,000, and the deaths exceeded 300.

Table 1: Shows The Confirmed Cases of Sars-Cov-2 In Iraq In The Provinces of Iraq The 7th Of June 2020.

<table>
<thead>
<tr>
<th>Province</th>
<th>Cases</th>
<th>Deaths</th>
<th>Recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baghdad</td>
<td>2,234</td>
<td>97</td>
<td>941</td>
</tr>
<tr>
<td>Al-Anbar</td>
<td>6</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Al-Qadisiya</td>
<td>15</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Babil</td>
<td>49</td>
<td>5</td>
<td>39</td>
</tr>
<tr>
<td>Basra</td>
<td>747</td>
<td>18</td>
<td>578</td>
</tr>
<tr>
<td>Thi Qar</td>
<td>96</td>
<td>4</td>
<td>72</td>
</tr>
<tr>
<td>Diyala</td>
<td>45</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Duhok</td>
<td>102</td>
<td>0</td>
<td>26</td>
</tr>
</tbody>
</table>

In Iraq, a high SARS-CoV-2 ministerial committee was established by the Iraqi Ministry of health to lead the efforts to control. The committee designed an official protocol (Figure 1A) for the treatment of SARS-CoV-2 and distributed it to hospitals. Lopinavir/ritonavir + ribavirin combination was at the top of the suggested therapies to be used in the treatment of SARS-CoV-2, and that was excellent from the evidence-based medicine point of view. However, the suggested treatment was not available at all in the country. The second suggested treatment was plasma therapy which it was impossible to offer to any patient needs treatment supposing that is an acceptable therapeutic option.
The second treatment option was Favipiravir which was supported by unpublished reference [Reference-31. A Trial of Favipiravir and Hydroxychloroquine combination in Adults Hospitalized with moderate and severe Covid-19 CLINICAL TRIAL PROTOCOL, King Abdullah International Medical research Center, Protocol V1 date April 5th 2020] (Figure-1C).

The SARS-CoV-2 is an enveloped non-segmented positive-sense RNA virus β-coronavirus (subgenus sarbecovirus, Orthocoronavirinae subfamily) with 96.2% of its genome is identical to a bat coronavirus RaTG13, and 79.5% of its genome is similar to SARS coronavirus. Therefore, bats, the natural host of many of the coronaviruses including SARS-CoV-like and MERS CoV-like viruses, are the most likely natural host of SARS-CoV-2, which was possibly transmitted to a human an intermediate host. SARS-CoV-2 is likely using angiotensin-converting enzyme-2 (ACE2) to infect humans. [1-4,7]. Table-2 summarizes the common features of SARS-CoV-2 that occurred in 55,924 cases in China and reported by Max Roser and Hannah Ritchie in February, 22, 2020. Figure 2 shows a sketch of SARS-CoV-2 appearance with electron microscope.
The first SARS coronavirus infection was causing respiratory failure in about 20% of patients; therefore, empiric treatments were justified including protease inhibitors (Lopinavir/ritonavir) in combination with ribavirin. Treatment of coronaviruses suggested that Lopinavir and ritonavir, protease inhibitors improved the outcome of MERS-CoV and SARS CoV patients. Chu et al (2004) reported the treatment of 41 patients with SARS with a combination of Lopinavir/ritonavir and ribavirin. The clinical and virological outcomes were compared with 111 patients treated with ribavirin monotherapy. Poor clinical outcomes including acute respiratory distress or death were significantly lower in the Lopinavir/ritonavir treated patients. The experimental work of Chan et al (2015) showed that treatment with Lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. Park et al (2019) studied the efficacy of ribavirin and Lopinavir/ritonavir as Post-exposure prophylaxis for healthcare workers exposed to patients with severe MERS-CoV pre isolation pneumonia. They found that therapy was associated with a 40% decrease in the risk of infection without the occurrence of severe adverse effects. Beta-coronavirus viral loads of a SARS-CoV-2 in a Korean patient were markedly reduced following Lopinavir/ritonavir treatment, while combined treatment with Lopinavir/ritonavir, arbidol, and Shufeng Jiedu Capsule (SFJDC, a traditional Chinese medicine) was associated with improvement in pneumonia caused by SARS-CoV-2 [10-15].

Figure 2: shows the chemical structure of Lopinavir/ritonavir.

Table 3: Information relevant to the clinical use of Lopinavir/ritonavir [1-3]

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<tr>
<th>Lopinavir/ritonavir (Kaletra) is a preparation with fixed dose</th>
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Remdesivir (GS-5734) is a nucleotide analog which was developed for the treatment of Ebola virus disease and Marburg virus infections. It attacks viral RNA-dependent RNA polymerase (RdRp) and causes in premature termination of viral RNA transcription. It can show antiviral activity against single stranded RNA viruses including respiratory syncytial virus [1-3].

Sheahan et al (2017) reported that Remdesivir can inhibit SARS-CoV and MERS-CoV replication in multiple in vitro systems, including primary human airway epithelial cell cultures with submicromolar IC_{50} values. According to Sheahan et al, Remdesivir was also effective against bat coronaviruses, pre pandemic bat coronaviruses, and circulating contemporary human CoV in primary human lung cells suggesting that Remdesivir has broad-spectrum anti-CoV activity. Sheahan et al also reported that in a mouse model of SARS-CoV early treatment with Remdesivir significantly reduced lung viral load and improved clinical signs of disease and respiratory function. Agostini et al (2018) reported that Remdesivir effectively inhibits human and zoonotic coronaviruses in vitro and in SARS-CoV mouse model. They showed that Remdesivir inhibits murine hepatitis virus (MHV) with similar 50% effective concentration values (EC_{50}) as SARS-CoV and MERS-CoV. Brown et al showed that Remdesivir has effective antiviral activity against SARS-CoV in primary human lung cells and both avian and porcine members harbor a native residue in the RdRp that confers resistance in beta-coronaviruses. However, Remdesivir is highly effective against porcine delta coronavirus. Remdesivir was used in the treatment of the first patient with COVID-19 in the USA and treatment was considered successful and probably stopped for the progression of pneumonia [16-19]. Figure 3 shows the chemical structure of Remdesivir.

<table>
<thead>
<tr>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea, nausea, and vomiting especially in children.</td>
</tr>
<tr>
<td>Tiredness and ashenia</td>
</tr>
<tr>
<td>Headaches</td>
</tr>
<tr>
<td>Muscle pains</td>
</tr>
</tbody>
</table>

**Possible serious side effects**

Pancreatitis, Injury, Hyperglycemia

**Use during pregnancy**

Probably safe, and use is common.

**Use with caution in**

Structural heart disease, Cardiac conduction abnormalities, Ischaemic heart disease, Cardiomyopathies

Chloroquine was thought to have an effect on SARS-CoV infection and spread which can be attributed to immunomodulatory effects, suppression of the production/release of TNF-α and IL-6, autophagy inhibition, and interference with the glycosylation of cellular receptors of SARS-Co. Chloroquine may act on entry and at post-entry stages of the COVID-19 infection in Vero E6 cells [20-22].

As early as 2004, in vitro inhibition of severe acute respiratory syndrome coronavirus by Chloroquine has been demonstrated by Keyaerts et al, and during February 2020, Gao, Tian, and Yang reported a benefit of Chloroquine phosphate in SARS-CoV-2 associated pneumonia [23-24]. Figure 4 shows the chemical structure of Chloroquine. Table-4 summarizes the information relevant to the clinical use of Chloroquine.

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**Table 4: Information Relevant To The Clinical Use Of Chloroquine [1-3]**

<table>
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</tr>
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<tbody>
<tr>
<td>Chloroquine is on the World Health Organization’s list of essential medicines which is the list of the medicines needed in a health system that are considered to be the safest and most effective.</td>
</tr>
</tbody>
</table>

**Antiviral Activities**

Chloroquine antiviral effects are attributed to increasing late Endosome or lysosomal pH, leading to impairment of the release of the virus from the endosome or lysosome, and thus preventing the release of virus genetic material into the cell and therefore preventing its replication. Chloroquine also inhibits or preventing viral RNA dependent RNA polymerase by acting as a zinc ionophore, allowing extra-cellular zinc to enter the cell.

**Administration**

Oral

**Common and Minor Side Effects**

Muscle problems, Gastrointestinal, Nausea, anorexia, vomiting, diarrhea, abdominal cramps, Skin rash and easy bruising, Pruritus, Headache, Legs and ankles swelling, Unpleasant metallic taste.

**Possible Serious Side Effects**

Blurred vision, Muscle weakness, Neutropenia, reversible agranulocytosis, and thrombocytopenia, Pancreatitis and aplastic anemia, Cardiomyopathy, Shortness of breath, Hearing impairment and tinnitus, Uncontrolled movements of tongue and face twitching.

**Possible Serious Side Effects**

Mental/mood changes including confusion, personality changes, unusual thoughts/behavior, depression, feeling being watched, hallucinating. Flue-like illness with high fever, severe chills, and persistent sore throat.
Baron et al [2020] emphasized that Teicoplanin was previously reported to be effective in inhibiting the first stage of MERS-coronavirus viral cycle in human cells, was also active against the SARS-CoV-2. In addition, Wang et al [2016] Teicoplanin can inhibit Ebola pseudovirus infection by blocking virus entry in the low micromolar range [25-26]. It is also able to block the MERS and SARS envelope Pseudotyping viruses.

Teicoplanin is a semi-synthetic glycopeptide antibiotic used in the prophylaxis and treatment of serious infections caused by Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus and Enterococcus facialis. It acts by inhibiting bacterial cell wall synthesis, and its spectrum of activity similar to vancomycin. Oral Teicoplanin has been shown to be effective in the treatment of pseudomembranous colitis and Clostridium difficile-associated diarrhea, with comparable efficacy with vancomycin [1-3]. Figure 5 shows the chemical structure of Teicoplanin.

Teicoplanin can be used in the doses suggested by Sato et al [2006] [27]. A loading dose of 400 or 800 mg can be given on the first day, followed by maintenance dose of 400mg. In areas where serial tests are available for asymptomatic patients, a dose of 400mg can be given for to days with aim of achieving early negative test and clearance of the virus, and thus reducing its spread [1-4].

A study treated two groups of SARS-CoV-2 patients and compared the effect of treatment with sixteen SARS-CoV-2 control patients. Six patients (First group) were treated with Hydroxychloroquine (200 mg, 3 times daily, for 10 days) plus azithromycin (500 mg on first day, followed by 250 mg daily for the next 4 days), 14 patients were treated with Hydroxychloroquine as a single drug. On the sixth day of treatment, 100% of patients treated with Hydroxychloroquine plus azithromycin (First group) experience virological cure. Only 57.1% of the patients treated with Hydroxychloroquine as a single drug (Second group) and 12.5% in the control group experienced virological cure (P< 0.001).

Recommendation
The early use of safe well-known therapeutic agents having the potential to control the virus such as azithromycin, and Teicoplanin can help in preventing milder cases from spreading the virus, and also may prevent the progression to serious pneumonia and significant respiratory distress. However, effective treatment for more severe cases can also be achieved by the early use of drug
combinations that may include Lopinavir/ritonavir + ribavirin + azithromycin + Teicoplanin, Remdesivir + azithromycin, + Teicoplanin. The addition of low dose Chloroquine can also be considered in patients with healthy hearts.

Acknowledgement
Some of the sketches this paper was published before in our previous publication and the author have their copyright.

Conflict of interests: None.

References
Antiviral Efficacies of FDA-Approved Drugs against SARS-CoV-2 Infection in Ferrets. mBio 11: e01114-20.


