RESUMEN

Introducción: La Enfermedad por coronavirus 2019 (COVID-19) causada por el virus SARS-CoV-2, con característica de infectar el tracto respiratorio causando un síndrome respiratorio agudo como paso inicial para ingresar a la célula huésped el virus usa los receptores ACE II y la proteína transmembrana TMPRSS2 para causar la infección, Por lo que se ha descrito diferentes tipos de fármacos para realizar su inhibición en el adhesión del paso inicial.

Metodología: Revisión no sistemática de artículos con la ayuda de palabras clave preestablecidas.

Resultados: En esta revisión presentaremos fármacos que inhiben este tipo de receptor, por lo tanto, estos medicamentos podrían considerarse candidatos potenciales para mitigar la propagación del SARS-CoV-2.

Palabras Clave: TMPRSS2; ACE II; COVID-19; 2019-nCoV; Coronaviridae.

ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus with characteristic of infecting the respiratory tract, causing severe acute respiratory syndrome. The virus uses the ACE II receptors and the transmembrane protein TMPRSS2 initial step to enter the host cell, this contribution described different types of drug, to perform its inhibition in initial step adhesion.

Methodology: Non-systematic review of articles with the help of preset keywords

Results: In this review we will present drugs that inhibitors of this type of receptor therefore these drugs could be considered potential candidates to mitigate the spread of SARS-CoV-2.

Keywords: TMPRSS2; ACE II; COVID-19; 2019-nCoV; Coronaviridae.
INTRODUCTION

The 2019 coronavirus disease epidemic (COVID-19) caused by the new SARS-CoV-2 virus has led to the spread of serious respiratory lung disease worldwide. According to Baltimore, this new virus belonging to the Coronaviridae family classified in group III, defined as a single-stranded RNA virus with a positive sense. It presents a generally large genome which could present mutations over time\(^{(1,2)}\). Several viruses in this family have been considered as infectious agents causing common colds, that is way they are in constant circulation in the human population. However, different viruses belonging to this family have appeared that have caused serious problems infecting thousands of people, such as (SARS-CoV) associated with Severe Acute Respiratory Syndrome in 2003, and (MERS-CoV)\(^{(3)}\) associated with Middle East Respiratory Syndrome in 2002.

Currently (July, 16th 2020) the new coronavirus has spread in 188 countries which has infected 13,744,743 people causing 588,383 deaths\(^{(4)}\) until today. The spread of this virus has increased significantly due to the type of transmission which has not yet reached a clear consensus; It has been said that this kind of virus has different forms of transmission: from animals to humans; from humans to animals; and from humans to humans; through contact; and respiratory droplets\(^{(5)}\). Furthermore, it is not certain that the virus is transmitted by air, however, the COVID-19 virus can be spread indirectly by contact with surfaces in its immediate environment or with objects that have been used by someone infected, highlighting that the viral particle can be stay on these surfaces for an estimated time\(^{(6)}\).

Based on the above, the specific route of transmission of natural reservoirs to humans continues in contradictions. The most accurate evidence believed so far is that pangolins are responsible for providing this transmission to humans. This shows us that the receptor-binding domain of the S protein of pangolin-CoV is almost similar to SARS-CoV-2\(^{(7)}\). Different studies have shown that the angiotensin-converting enzyme 2 (ACE II) plays an important role as a receptor for SARS-CoV-2 in the binding of eukaryotic animal cells in the vicinity to infect, however, it has been intensified that the serine TMPRSS2 protease as a crucial adjuvant (cofactor) for the binding of this virus peak protein\(^{(8)}\) converting these receptors as potential candidates for the development of white molecules that prevent the entry of the virus and thus counteract the pandemic caused by SARS-CoV-2. Therefore, this article identifies some receptor inhibitor molecules that contribute to virus adhesion in human host cells.

MATERIAL AND METHODS

A non-systematic review of clinical cases, original and review articles was carried out in indexed databases such as PubMed; ScienceDirect; Springer; and OVID in first, and second language from 2005-2020 mainly. For this research paper, The MeSH terms used for the article search and selection process were TMPRSS2, ACE II, COVID-19, 2019-nCoV, New treatment strategies, SARS-CoV-2, and Coronaviridae. Only the articles that had the MeSH terms were selected. This search strategy consisted of combining the MeSH terms as exclusion or inclusion criteria to make the search process more efficiently.

RESULTS AND DISCUSSION

The TMPRSS2 receptor has been studied as one of the main receptors for target cells with the assistance of ACE II. For this reason, different drugs that inhibit these two receptors have been tested, in order to counteract the adherence SARS-Cov-2 in human host cells.

Camostat mesilate and Nafamostat

Nowadays, Camostat has a wide range of uses. That is why this drug could be considered as one of the most promising candidates for the treatment of respiratory infections caused by SARS-CoV-2 today. Since this drug achieves the blocking of serine protease enzymes. In fact, this inhibitor was approved in Japan as a treatment of chronic pancreatitis, and postoperative reflux esophagitis \(^{(9)}\). According to studies, and clinical trials, Camostat can block the entry of the SARS-CoV2 virus inside the target cell. This has been demonstrated by in vitro cell test where this drug obstructs the adherence of the SARS-CoV virus, and the SARS-CoV-2 glycoprotein, if it is provided at a concentration of 10 μM\(^{(10)}\). On the other hand, different research suggests Nafamostat, a serine protease inhibitor, as another candidate drug for combating Covid-19, since it is known that Nafamostat blocks MERS-CoV virus infection in vitro by inhabiting the activity of TMPRSS2 thus achieving a 100-fold reduction in viral entry at a concentration as low as 1 nM. This means that it is more effective than Camostat. That said, Nafamostat could contribute to blocking the entry of the new coronavirus into cells close to infecting it. This is how Nafamostat becomes another interesting drug for studies against SARS-COV-2\(^{(11)}\).

Bromhexine Chlorhydrate

It is a mucolytic agent used in the treatment of respiratory disorders associated with excessive and viscous mucus. It
was previously used for the treatment of influenza virus, and coronavirus infections as an inhibitor of TMPRSS2. Bromhexim contributed significantly to the inhibition of trypsin-like proteases, expressed in the human respiratory tract of influenza, such as the SARS-CoV and MERS viruses\(^{(12)}\).

According to the reports presented by Shen et al\(^{(13)}\), this drug could be used for treatment of infections caused by viruses of the coronaviridae family that cause severe respiratory infections. They suggest that these drugs can be used to treat patients who are asymptomatic of covid-19, in order to prevent the virus spread, which would cause multiple effects in the most vulnerable population who would suffer an infection by 2019-nCoV.

Morpholine phosphorodiamidate oligomers linked to peptide

Morpholine phosphorodiamidate oligomers (PPMO) are synthetic antisense molecules. These molecules target the genetic code within the virus. They avoid the virus reproduction ability since they can interfere with gene expression by sterically blocking complementary RNAs\(^{(14)}\). This synthetic compound interferes in the correct splicing in pre-mRNA of TMPRSS2 receptor, causing the mature mRNA production without the presence of exon 5. This leads to the incorrect genetic expression of the receptor. That is why these synthetic agents resemble single-stranded DNA, and can easily enter the target cell to change the pre-mRNA splicing pattern.

There are in vitro results that show us this molecule could contribute to the drastic reduction of SARS-CoV-2 in cell cultures. In others words, this molecule can reduce the contagion rate in a range of time of 16, 24, and 48 hours after the cell cultures were exposed to the virus\(^{(16)}\).

Polyamide

Polyamide is a type of polymer that contains amide-type bonds. Many researches have used this polymer to develop different therapeutic treatment. Also, this polymer has been used to coat medical devices as it functions as an antimicrobial agent in the clinic devices\(^{(17)}\). In this research, polyamide is suggested as another candidate drug to counteract respiratory infections caused by SARS-CoV-2 since its compounds moderately block the TMPRSS2 receptor; Therefore, this drug may moderately contribute to the non-adherence of some viruses that use this receptor as a route of entry to host cells, such as the current SARS-CoV-2\(^{(18-19)}\).

Rubitecan, Lorazepam, Zinc15 and Ascorbic Acid

Rubitecan is an enantiomer 20 (S) enantiomer 9-nitrocampothecin (9-NC). Its main function is to act as an inhibitor of tumor activity, presenting a blocking molecule that prevents cell replication. On the other hand, lorazepam is a drug from the benzodiazepine family, which is given as a treatment for short-term insomnia, hypnotics, and muscle spasms\(^{(20)}\). These target molecules have been tested in silico by docking and molecular dynamics. The test result showed a high binding affinity between these drugs (ligands) and the TMPRSS2 receptor (target molecule) Also, this test result could highlight a relatively low energy value that showed us that these molecules could be candidates to counteract the entry of the virus into the cell.

Likewise, the Zinc15 molecule has been studied as a potential inhibitor of the entry pathway through the receptor of the transmembrane protein TMPRSS2, which in molecular coupling has a very high affinity for this protein\(^{(21)}\). Also, Ascorbic acid or vitamin C can work as a weak antihistamine agent, which in turn contributes to the symptoms of lower respiratory infections. The inhibition of ACE II receptor in turn contributes to the non-expression of TMPRSS2, thus helping to mitigate flu symptoms and, in turn, vitamin C could be considered as another alternative to treat critically ill patients with covid19\(^{(22)}\).

The aforementioned information highlights different candidate molecules that may be targets for inhibiting the spread of 2019-nCoV infection. The Table 1 shows us another summary about the characteristics of these drugs that could be successful to reduce SARS-CoV-2 infection.

CONCLUSION

All the drugs mentioned in this review could contribute to the aim of achieving the actions that prevent the entry of the SARS-CoV-2 virus by serine protease. Although the mechanisms of action and efficacy of these drugs require more rigorous studies to have full certain of their results in human beings, they cannot be ruled out as possible candidates, on the contrary, they must be taken into account as possible useful drugs in the treatment of COVID 19 patients.
Table 1. Characteristics of drugs that can be used to treat 2019-ncov.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Metabolic pathways involved</th>
<th>Essays trials</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camostat mesilate</td>
<td>TMPRSS2 receptor</td>
<td>block the activation of trypsinogen to trypsin and the path of the inflammatory cascade.</td>
<td>In vitro In vivo</td>
<td>Eosinophilic pneumonia, skin rash, itching, nausea and diarrhea.</td>
</tr>
<tr>
<td>Nafamostat</td>
<td>TMPRSS2 receptor</td>
<td>Inhibits the activities of proteases, esterase in the complement system, and factors in the coagulation system</td>
<td>In vitro In vivo</td>
<td>Agranulocytosis, hyperkalemia, anaphylaxis, dyspnea and cardiac arrest.</td>
</tr>
<tr>
<td>Bromhexine Chlorhydrate</td>
<td>TMPRSS2 receptor</td>
<td>Acts within the mucus-secreting cells and disrupts the structure of acid mucopoly saccharide fibres</td>
<td>In vitro In vivo</td>
<td>Headache, dizziness, nausea, rash, diarrhea, vomiting and indigestion.</td>
</tr>
<tr>
<td>PPMO</td>
<td>TMPRSS2 receptor</td>
<td>Block complementary RNAs of the pre-mRNA of the TMPRSS2 receptor</td>
<td>In vitro</td>
<td>No data available</td>
</tr>
<tr>
<td>Ascorbic Acid</td>
<td>ACE II and TMPRSS2 receptor</td>
<td>Works as an antioxidant against infections, collagen synthesis and detoxifying reactions</td>
<td>In vitro</td>
<td>Acute liver injury or jaundice.</td>
</tr>
<tr>
<td>Rubitecan</td>
<td>TMPRSS2 receptor</td>
<td>block via topoisomerase, DNA and RNA synthesis in dividing cells</td>
<td>In silico In vitro</td>
<td>Vomiting, cough, fatigue and pharyngeal mucositis</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>TMPRSS2 receptor</td>
<td>Inhibits benzodiazepine receptors in the chloride channel</td>
<td>In silico</td>
<td>Agitation, delirium, insomnia, muscle spasms, deep respiratory, depression, coma, and death</td>
</tr>
<tr>
<td>Zinc15</td>
<td>TMPRSS2 receptor</td>
<td>Inhibits the activities of proteases</td>
<td>In silico In vitro</td>
<td>Rash, itching, eye redness, ocular irritation and skin irritation</td>
</tr>
</tbody>
</table>

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