STUDY OF AVAILABLE ANTIVIRAL TREATMENTS FOR COVID-19 DURING PREGNANCY

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Abstract

Since the end of the year 2019, mankind has been confronting with the COVID-19 pandemic. Complex measures have been taken to solve this problem and the aim of this study is to summarise the results of research on the most used antiviral treatments for COVID-19 diagnosed in pregnant women. The specialty literature review was conducted by searching the PubMed (National Library of Medicine, Washington, DC) and Embase (Elsevier) databases. In the initial search in databases we used a combination of the following keywords: “COVID-19”, “SARS-CoV-2”, “pregnancy” and “therapy”. Clinical trials were identified using the search term "COVID-19" and the generic names of the drugs on ClinicalTrials.gov and International Clinical Trials Registry Platform (ICTRP) of WHO. Corresponding to the objectives of our research, we found articles and studies about antiviral drugs which act as: protease inhibitors (lopinavir/ritonavir, darunavir/cobicistat), RNA polymerase inhibitors (remdesivir, favipiravir, ribavirin), umifenovir, antimalarial drugs (chloroquine, hydroxychloroquine) and others. Summarising what is currently known about the antiviral treatment of COVID-19 during pregnancy, we can conclude that, at this time, no antiviral drug is undoubtedly effective in the fight against SARS-CoV-2; the experience gained so far, leads to the idea that treatment schemes must combine several methods and drugs to be successful; a national or even international register should be set up to report situations where a medicine has been administered to a pregnant woman to monitor for side effects; pregnant women should also be included in studies, under rigorous conditions and after a clear demonstration of the effectiveness of medicines.

Rezumat

De la sfârșitul anului 2019, omenea se confruntă cu pandemia COVID-19. Au fost luate măsuri complexe pentru a rezolva această problemă, iar scopul acestui studiu este de a face o sinteză a rezultatelor cercetărilor privind cele mai utilizate tratamente antivirale pentru COVID-19, la femeile gravide. Revizuirea literaturii a fost efectuată prin căutarea în bazele de date PubMed (Biblioteca Națională de Medicină, Washington, DC) și Embase (Elsevier). În căutarea inițială din bazele de date a fost folosită o combinație de cuvinte cheie: „COVID-19”, „SARS-CoV-2”, „sarcină” și „terapie”. Studiile clinice au fost identificate folosind termenul de căutare „COVID-19” și denumirile generice ale medicamentelor de pe ClinicalTrials.gov și Platforma internațională de înregistrare a studiilor clinice (ICTRP) a Organizației Mondiale a Sănătății (OMS). Corespunzând obiectivelor cercetării desfășurate, au fost găsite articole și studii despre medicamente antivirale care acționează ca: inhibitori de protează (lopinavir/ritonavir, darunavir/cobicistat), inhibitori de ARN polimerază (remdesivir, favipiravir, ribavirin), umifenovir, medicamente antimalarice (chloroquină, hidroxicloroquină) și altele. Rezumând ceea ce se știe în prezent despre tratamentul antiviral al COVID-19 în timpul sarcinii, putem concluziona că în acest moment niciun medicament antiviral nu este, fără îndoială, eficient în lupta împotriva SARS-CoV-2; experiența acumulată până acum conduce la ideea că schemele de tratament trebuie să combine mai multe metode și medicamente pentru a avea succes; ar trebui creat un registru național sau chiar internațional pentru a raporta situațiile în care un medicament a fost administrat unei femei însărcinate pentru a monitoriza efectele secundare; femeile însărcinate ar trebui, de asemenea, să fie incluse în studii, în condiții rigoroase și după o demonstrație clară a eficacității medicamentelor.

Keywords: SARS-CoV-2, COVID-19, treatment, pregnancy
Complex measures have been taken to solve this problem, starting with prevention and continuing with the treatment and recovery of infected patients. Given that it is a viral infection, treating it has proved difficult and the medical world is trying to approach it in several ways. Therefore, we can differentiate between antiviral treatments and immune mechanism-based treatments, to which some important adjunctive treatments have been added [2].

A number of drugs, most of which are already known in the medical world, have been proposed to be tested for COVID-19 therapy [2].

All categories of the population are exposed to the risk of infection, but the specificity of each group is raising additional problems in finding an optimal treatment. Among the population groups considered to be at high risk, the one which represents pregnant women is individualized. For this group, there are special problems due to the fact that many drugs can be administered only with restriction or simply cannot be administered due to the risk of harming the foetus and mother. Often, pregnant women are ruled out from clinical studies precisely for these reasons. Accumulating data on the treatment for pregnant women is a much slower and difficult process. The aim of this study is to summarise the results of research on the most used (so far) antiviral treatments for COVID-19 in pregnant women.

Materials and methods

The specialty literature review was conducted by searching the PubMed (National Library of Medicine, Washington, DC) and Embase (Elsevier) databases. The keywords for initial databases searches included a combination of the following key words: “COVID-19”, “SARS-CoV-2”, “pregnancy” and “therapy”. We limited our investigation to English-language journals. We also reviewed additional relevant articles which were identified from the referenced citations. Active clinical trials were identified using the disease search term “COVID-19” and the generic names of the drugs used in the therapy of this disease on ClinicalTrials.gov and International Clinical Trials Registry Platform (ICTRP) of WHO.

For each type of drug we found articles that were analysed by two reviewers, only the relevant ones being selected. In order to be included in the review, the articles had to have the approval of both reviewers. This systematic review was structured according to the PRISMA guidelines but the pre-existing protocol cannot be entirely used because, related to some aspects, we only found few published data. The lack of data due to the fact that many studies are still ongoing, forced us to include in our review all types of studies: prospective, retrospective, case control and other systematic reviews.

Results and discussion

From the very beginning it is obvious that the vast majority of treatment studies exclude pregnant women from the start. For example, on the ClinicalTrials.gov website accessed on 21.10.2020, 2374 studies on treatments for COVID-19 are listed, which are in different stages of development, but of these only 26 (1%) refer to or include pregnant women [3, 4].

Regarding preventive treatment, the gold standard is vaccination and it is known that in many countries around the world researchers are trying to obtain effective vaccines against SARS-Cov-2. So far, however, it has not been possible to obtain an effective vaccine. Although pregnant women would be ideal candidates for preventive treatments, they are excluded from most trials. This fact has been notified by the scientific world and attempts are being made to reintroduce pregnant women into studies by reformulating conditions for participation so that this can be done in conditions of maximum safety.

Medications such as emtricitabine plus tenofovir, hydroxychloroquine or zinc supplements, vitamin C or vitamin D have been considered for pre-exposure prophylaxis, but so far there is no evidence that they are effective [5].

Also for post-exposure prophylaxis, several types of drugs have been tested, such as: chloroquine, hydroxychloroquine, lopinavir/ritonavir, nitazoxanide, vitamin D and B vitamins or immunological therapies with monoclonal antibodies or convalescent plasma, but the results obtained so far are not convincing [5].

From the researched databases we found that, until now, only one non-randomized phase 3 interventional study referring to the use of hydroxychloroquine, performed in India on 325 cases, has been completed, with yet unpublished results [6].

Regarding the treatment of the disease itself, it can be systematized from the beginning in: antiviral treatment, immunological treatment and adjuvant treatment. Already known drugs, which are likely to be effective in this situation, have often been proposed and tested for the treatment of COVID-19.

Along with articles on case reports or clinical trials from research databases, we identified five previous reviews by Favilli A et al., Li L et al., D’Souza R et al., Sanders et al. and Pastik KA et al., that drew attention upon several groups of antiviral drugs [7-11].

Protease inhibitors

Lopinavir and Ritonavir

They have been known for almost 25 years (lopinavir since 1995 and ritonavir since 1996). Both lopinavir and ritonavir belong to the class of first-generation protease inhibitors (inhibits 3-chymotrypsin-like protease).

Ritonavir further inhibits the enzyme that contributes to the metabolism of lopinavir and thus makes their combination beneficial, as this may decrease the
doses of lopinavir, allowing to the same effect to be obtained, with reduced side effects. The combination of lopinavir/ritonavir (LVR/r) was originally used in the treatment of HIV infection and was suggested for the treatment of COVID-19 precisely because of the similarities between some areas of the viral genome. In addition, it has been used in the treatment of SARS-CoV-1 infection, with encouraging results.

Regarding the use in pregnant women, there are older safety profile studies, such as that of Roberts SS et al. in 2009 on 955 cases, which showed that the prevalence of malformations in children belonging to mothers treated with LVR/r did not significantly increase, compared to that of pregnant women in the general population [12]. This would be due to the fact that it would not cross the placental barrier in significant quantities.

Regarding the evolution of pregnancy, although some studies stated that there is a risk of premature birth, others denied it. We quote the study of Koss et al., completed in 2014, which included 179 HIV-positive patients treated with LVR/r and who did not find a significant statistical difference for this risk [13].

Adverse effects were also monitored by entering data in the Antiretroviral Pregnancy Registry (APR), where over 3000 cases with lopinavir treatment during pregnancy have been recorded and over 5000 cases of ritonavir have been analysed, without finding any difference in regard to the incidence rate of foetal malformations compared to the general population [14].

Medicines are classified in the Australian Therapeutic Goods Administration (AU TGA) in pregnancy category: B3, while in the United States Food and Drug Administration (US FDA) they are classified in pregnancy category: N (Not assigned).

Regarding the treatment for COVID-19, it was initially used in China; the first unfavourable data regarding its effectiveness also came from there, showing that no benefits were registered by using it in hospitalized patients with severe forms of disease, compared to the standard care [15].

Some authors have shown that in order to be effective, it is essential to administer this treatment in the first 7 - 10 days of infection during peak viral replication in parallel with SARS-CoV-1 infection [11, 16]. This could partially explain the ineffectiveness shown in the treatment of severe forms. The most used treatment regimen was the administration of a total dose of 400 mg/100 mg two times per day for 14 days. Results of the WHO SOLIDARITY trial, which included 1399 cases in the branch for LVR/r, were recently reported (interim), on 15th October. The report was disappointing, showing that mortality at 28 days, the need for assisted ventilation and the duration of hospitalization were not different from those of the control group, but this data must be carefully analysed and verified [17].

However, there is an ongoing European study, DISCOVERY, not yet completed, and the search on ClinicalTrials.gov revealed another 75 studies on this subject, 10 of which were completed and 1 finalized, with results soon to be published.

**Darunavir and Cobicistat**

For this association, the mechanism of action is similar to LVR/r. The reason for which these drugs are not recommended for the treatment of HIV in pregnant women, namely the considerably lower exposures of darunavir and cobicistat during the second and third trimesters, makes it interesting for the treatment of COVID-19 (which is generally not transmitted transplacentally).

Darunavir is classified in AU TGA category B2 and US FDA category N (Not classified yet). However, the in vitro tests performed by the manufacturer regarding the action on SARS-CoV-2 were disappointing. "Darunavir showed no activity against SARS-CoV-2 at clinically relevant concentrations (EC50 > 100 μM). These data do not support the use of darunavir for the treatment of COVID-19." [18].

**RNA polymerase inhibitors**

**Remdesivir**

Known for more than 10 years, remdesivir is a 1'-cyano-substituted adenosine nucleotide analogue prodrug created by Gilead Sciences Inc., who declared "The research that led to remdesivir began as early as 2009, with research programs under way in hepatitis C (HCV) and respiratory syncytial virus (RSV).” [19]. As a mode of action is a nucleotide prodrug that is metabolized into an analogue of adenosine triphosphate that inhibits viral RNA polymerases. Especially after in vitro or animal tests, it is considered an antiviral drug with broad-spectrum activity against RNA viruses in several families, including *Coronaviridae*, *Paramyxoviridae* and *Filoviridae* [20- 22].

Together with a metabolite of GS-441524, remdesivir had promising results against SARS-CoV-1, MERS virus and feline infectious peritonitis virus, but disappointing in the treatment of Ebola and Marburg virus [23].

Regarding the experience for its use in pregnant women in many works, it is quoted the study of Mulangu S et al. from 2019, about the treatment of Ebola virus disease. Analysing carefully, we can notice that in this study it is mentioned that the recruiting of the patients for the arm with remdesivir treatment and the one with triple monoclonal antibody (Zmapp) treatment were stopped, after the intermediate evaluations, so only 6 pregnant patients received remdesivir and their data are not analysed separately [24].

In fact, Gilead Sciences Inc. states in the sheet for the authorization of Veklury® for emergency use (Emergency Use Authorization - EUA) of health care providers updated on 08.2020 “No adequate and well-controlled studies have been performed on the use of Veklury® (remdesivir) in pregnant women.
Veklury® should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and foetus.” [25]. In nonclinical toxicity studies, remdesivir demonstrated no adverse effect on embryofetal development when administered to gestational animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were 4 times (rats and rabbits) the exposure in humans at the recommended human dose (RHD) [25]. Remdesivir is classified in AU TGA category B2 and US FDA category N (Not classified yet). Initial studies on the use of remdesivir in the treatment of COVID-19 (at any stage of the disease) have had encouraging results. Grein J et al., on 53 patients with severe forms who were included in the compassionate use system in which clinical improvement was observed in 68% of patients [26]. Beigel J et al., in a double-blind study, a randomized, placebo-controlled trial of 1,062 patients, of whom 532 received remdesivir, obtained data showing a slight decrease in mortality and a shortening of the time of recovery without a significant rate of adverse effects [27]. The suggested adult dose is 200 mg intravenously on day 1, followed by 100 mg daily for a total of 5 days (with extension to 10 days if there is no clinical improvement and in patients on mechanical ventilation or ECMO- Extracorporeal membrane oxygenation). On 01.05.2020, the FDA issued an Emergency Use Authorization (EUA) for the use of remdesivir in the treatment of COVID. Due to the lack of concrete data on administration to pregnant women, it was accepted only for compassionate use, both in USA and Europe. Studying the literature in the PubMed database we have only found 5 communications totalling a number of 11 cases in which remdesivir was administered to pregnant women, namely 3 case reports and two series of cases, one with 5 and one with 3 reported cases [28-32], as presented in Table I.

### Table I

Reports regarding the use of remdesivir in pregnant women

<table>
<thead>
<tr>
<th>No.</th>
<th>Authors</th>
<th>Article title</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>McCoy JA et al.</td>
<td>Compassionate use of remdesivir for treatment of severe coronavirus disease 2019 in pregnant women at a United States academic center.</td>
<td>5</td>
</tr>
<tr>
<td>2.</td>
<td>Igbinoja I et al.</td>
<td>Use of remdesivir for pregnant patients with severe novel coronavirus disease 2019</td>
<td>3</td>
</tr>
</tbody>
</table>

From the current data, the use of remdesivir during pregnancy was beneficial, given the favourable evolution in all treated patients, although these were severe or even critical cases. There were also no adverse foetal effects. Given the small number of cases and the fact that studies are not standardized, all these aspects remain in the spotlight. All data are presented in Table II.

### Table II

Clinical data of cases treated with remdesivir

<table>
<thead>
<tr>
<th>No. of case</th>
<th>Age of the patient [years]</th>
<th>Gestation age [weeks]</th>
<th>Coexisting pathology</th>
<th>Severity of COVID-19*</th>
<th>Maximum level of respirator support required</th>
<th>Days of symptoms before remdesivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>16</td>
<td>Asthma</td>
<td>Severe</td>
<td>Nasal cannula</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>28</td>
<td>Hyper-tension Diabetes</td>
<td>Critical</td>
<td>Mechanical ventilation</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>26</td>
<td>Asthma</td>
<td>Critical</td>
<td>Mechanical ventilation</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>31</td>
<td>Hyper-tension Diabetes</td>
<td>Critical</td>
<td>Mechanical ventilation</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>31</td>
<td>Immuno-suppression</td>
<td>Severe</td>
<td>Nasal cannula</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>34</td>
<td>Cholestasis</td>
<td>Severe</td>
<td>Mechanical ventilation</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>25</td>
<td>Seasonal allergies</td>
<td>Severe</td>
<td>Nasal cannula</td>
<td>?</td>
</tr>
<tr>
<td>8</td>
<td>29</td>
<td>25</td>
<td>Diabetes Asthma</td>
<td>Severe</td>
<td>Non rebreather</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>39</td>
<td>34</td>
<td>Obesity class III</td>
<td>Severe</td>
<td>Nasal cannula</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>35</td>
<td>22</td>
<td></td>
<td>Critical</td>
<td>Mechanical ventilation</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

960
Despite these encouraging results, an important question regarding the use of remdesivir in the treatment of COVID-19 is raised by the results of the WHO SOLIDARITY trial study which included 2743 cases in the arm for remdesivir and which showed that mortality with remdesivir was 301/2743 vs. 303/2708 in the control group (RR = 0.95, p = 0.50) and neither the need for assisted ventilation nor the duration of hospitalization were significantly different from those of the control group [17]. However, there are many other studies in progress or in the finalization phase that can bring new data. A study entitled “Role of Investigative Therapies Alone or in Combination to Treat Moderate, Severe and Critical COVID-19 in Pakistan Procedure: Therapeutic Plasma exchange Biological: Convalescent plasma, tocilizumab, remdesivir, Mesenchymal stem cell therapy” was recently completed in Pakistan on 600 cases, starting from the idea that the combination of several types of treatments can bring better results [33].

Favipiravir
Favipiravir is another member of RNA polymerase inhibitors group which is being evaluated in clinical trials for the treatment of COVID-19. From the chemical point of view, it is a modified purine analogue. It was discovered by Toyama Chemical Co. in Japan and approved for use in 2014. It has been used for the treatment of influenza and it seems to be also effective for Ebola virus disease, Lassa virus disease and rabies [34].

In a randomized trial completed in Russia, the rate of viral RNA clearance from upper respiratory tract specimens at day 5 was higher with favipiravir compared with standard of care rate 62 versus 36 percent [35]. Also, in a non-randomized study finalized in China, the treatment with favipiravir was associated with faster rates of viral clearance (median time to clearance 4 versus 11 days) and more frequent radiographic improvement (in 91 versus 62 percent by day 14) compared with lopinavir-ritonavir [36]. The problem with its administration in pregnancy is that it’s known to have a teratogenic effect, so it is not recommended for pregnant women, while for men it is not recommended to conceive if they are under treatment or at least 7 days after the end of treatment [37, 38].

Ribavirin
Ribavirin was synthesised for the first time in 1972 and its most successful derivative taribavirin in 1973. It is a guanine analogue and it is another antiviral agent which acts by inhibiting viral RNA-dependent RNA polymerase. In combination with interferon, it’s used for the treatment of chronic hepatitis C. Although it has been shown to be active against corona viruses, the therapeutic dose is close to or above the toxicity limit.

In a systematic review about the use of ribavirin for the treatment of SARS, it was found that the results were inconclusive in 26 of the 30 reviewed studies. In addition, there were evidences of haematological adverse effects and liver toxicity [39]. Due to the results of animal studies showing significant teratogenic and/or embryocidal effects in all exposed animal species, ribavirin is considered teratogenic and is therefore contraindicated during pregnancy (it is in Category X of the US FDA Pregnancy drug classification and in AU TGA) and even to men whose partners may become pregnant.

Because there were no data on humans, since 2003, in the United States it was released the Ribavirin Pregnancy Registry, where accidental exposure to pregnancy can be documented and monitored [40]. What is also interesting is that an ad interim analysis of potential teratogenicity of ribavirin at midpoint of enrolment (after enrolment of 272 pregnant women) was published in 2017, reporting 7 new-born babies with birth defects among 85 live births of directly exposed women. Based on that data, authors of this analysis concluded “preliminary findings do not suggest a clear signal of human teratogenicity for ribavirin” [41].

Umifenovir
Umifenovir is another type of antiviral agent with a unique mechanism of action. Studied on the influenza virus, umifenovir intervenes in the S protein/ACE2 interaction and prevents the entry of the virus into cells by inhibiting membrane fusion of the viral envelope and so prevents the infection of the cell [42].
This drug was created by researchers in Russia in 1993 and has been used under the name Arbidol® for about 25 years for a variety of diseases caused by enveloped and non-enveloped RNA and DNA viruses, including Flavivirus, Zika virus, foot-and-mouth disease, Lassa virus, Ebola virus, herpes simplex, hepatitis B and C viruses, chikungunya virus, reovirus, Hantaan virus and coxsackie virus B5 [43]. The fact that it is considered a broad-spectrum antiviral led to the idea of testing it against COVID-19 as well.

In a nonrandomized study on 67 patients’ with COVID-19, from China, umifenovir treatment was associated with lower mortality rates (0% [0/36] vs. 16% [5/31]) compared with patients with standard care [44]. Umifenovir is classified in the US FDA as C category. The usual dose was 200mg orally every 8 hours and the average duration of treatment was 8 days [11]. At present there are many ongoing clinical trials which further evaluate the efficiency of umifenovir for the treatment of COVID-19.

**Antimalarial drugs**

A special group of antivirals is represented by antimalarials. Although high hopes were initially attached to this group, it now tends to be excluded from the therapeutic arsenal for COVID-19.

This group includes chloroquine, chloroquine phosphate, hydroxychloroquine which have been used as antimalarials since the interwar period. Chloroquine was discovered in 1934 by Hans Andersag as a quinine analogue and marketed as Resochin® and the derivative hydroxychloroquine (more effective and with fewer side effects) during World War II. Due to its immunomodulatory properties, hydroxychloroquine has also been used as an antirheumatic in rheumatoid arthritis and lupus erythematosus [49].

Over time, drugs in this group have proven broad-spectrum antiviral properties in clinical trials even on HIV, MERS-CoV, SARS-CoV even in lower doses than those required in the antimalarial treatment [45]. The mode of action is through several mechanisms: it inhibits the receptor necessary for viral penetration in the body; because they are alkaline substances they increase the intracellular pH especially in some organites and nucleus where are concentrated, blocking the activity of ACE2 receptor that participates in viral replication; they block the production and release of TNF-alpha and IL-6; and by inhibiting lymphocyte differentiation in Th17 type cells they reduce the cytokines “storm” [7].

Some initial studies have shown that chloroquine and hydroxychloroquine have an effect before (for preventive purposes) and after infection of cells with SARS-CoV-2 (curative purpose) [46, 47].

Over time, a number of data on the use of chloroquine and hydroxychloroquine in pregnancy have been gathered, but data on the use in pregnant women with COVID-19 are currently just being collected.

The majority of existing data on their use in pregnant women refer to the treatment of malaria. It is known that it crosses the placental barrier and persists for a long time in the body (the half-life is up to 30 days for chloroquine and up to 60 days for hydroxychloroquine) [48]. Animal studies have shown that in foetuses it accumulates in the eyes, ears and adrenal cortex, at very high doses they can cause microphthalmia or anophthalmia, and also those they can cause genetic mutations through chromosomal damage [48].

In “Chloroquine and hydroxychloroquine during pregnancy: What do we know?” published in 2020, Lacroix I et al. quoted three studies on chloroquine exposure during the first trimester of pregnancy comprising 169, 130 and 774 patients who did not show an increase in foetal risks, and for hydroxychloroquine two meta-analyses (Kaplan et al., 2015 and Guillotin et al., 2018) which similarly did not show an increase in foetal impairment [48]. However, hydroxychloroquine is classified in Pregnancy category D in Australia and N (not assigned) in the USA.

The proposed regimen for COVID-19 treatment for Chloroquine is 1 g orally once in the first day of treatment and then 500 mg once daily for 4 – 7 days depending on the clinical response [11].

There is no agreement regarding the optimal treatment scheme with hydroxychloroquine. Several schemes have been tried: administration of 800 mg orally once on the first day and then 400 mg once a day for 4 days, or 400 mg every day for 5 days or 400 mg twice a day for the first day and then 200 mg twice a day for 4 days [11].

Although the previous studies show that they are generally well tolerated, chloroquine and hydroxychloroquine treatments have some side effects: retinopathy, hyperglycaemia, neurological defects and cardiac problems (arrhythmia and QT prolongation) [48]. However, new data suggest that they do not provide a clinical benefit for patients with COVID-19 or, even worse, the risks are higher [50, 51].

In a number of important ongoing studies, the recruitment of patients for hydroxychloroquine treatment was discontinued due to intermediate evaluations that showed a lack of efficacy in reducing mortality. This category included RECOVERY studies in the UK and the SOLIDARRITY study initiated by WHO.

In addition, on 15th June 2020, the provisional authorization granted by the FDA was suspended. One problem in using these drugs would be the sum of negative effects at the cardiac level with those given by the disease itself or the associated drugs.

**Other drugs**

From the multitude of substances that are currently being studied for their antiviral action we mention nitazoxanide and camostat mesylat.
Nitazoxanide, previously used as an antihelminthic agent, has proved an in vitro broad antiviral activity and is known to have a relatively favourable safety profile [11]. A study published by Calderon M et al. on 17 pregnant women reported positive results [52]. Camostat mesylate, used in Japan for the treatment of pancreatitis, also proved an antiviral activity in vitro by preventing the virus entry into the cells, through inhibition of a host serine protease [11].

Any review is by necessity selective. There are many more drugs or treatment methods in the attention of the medical world. A recent comprehensive study which analysed the data related to therapeutic agents and vaccines that could be candidates for the treatment of COVID-19 reported more than 130 patients and more than 3000 potential small molecule drug with potential activity against human coronaviruses [53]. To solve the global problem generated by COVID-19 studies must continue until the optimal solution is found.

Conclusions

Although efforts have been made, so far no antiviral drug has been found to be undoubtedly effective in the fight against SARS-CoV-2. The experience gained so far is leading to the idea that treatment regimens must combine several methods and medications to succeed.

A national or, even better, international register should be created, for each drug, to report the situations in which it was administered to pregnant women, with the purpose of monitoring possible side effects. In order to benefit from treatments, pregnant women should also be included in studies, under rigorous conditions and after a clear demonstration of the effectiveness of the drugs.

Conflict of interest

The authors declare no conflict of interest.

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