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European Journal of Pharmacology 887 (2020) 173467

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Full length article

What to expect from different drugs used in the treatment of COVID-19: A study on applications and *in vivo* and *in vitro* results

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ARTICLE INFO

Keywords:
Chloroquine
Antivirals
Dexamethasone
Ivermectin
Anticoagulants

ABSTRACT

The end of 2019 was marked by the emergence of a new type of coronavirus (SARS-CoV-2), which has killed more than 240,000 people around the world so far. Several clinical studies are being performed to test possible drugs in response to the COVID-19 outbreak; however, there is still no treatment that is completely effective. Our goal in this paper is to bring together the results of main studies carried out with different drugs in order to help spread the knowledge about possible treatments for COVID-19 that have been suggested so far.

1. Introduction

In the first half of April, the world reached catastrophic numbers due to the spreading of the COVID-19 pandemic. At a global level, more than 3.4 million people have been infected and more than 240,000 have died (WHO, 2020a). The virus has reached almost all the countries in the world and its spread has been proven to occur mainly through saliva spray disseminated by infected patients who are often asymptomatic (Heymann and Shindo, 2020; Xu et al., 2020).

Members of the *Coronaviridae* family are viruses with positive-sense, single stranded ribonucleic acid (RNA) genomes (Modrow et al., 2013). Currently, some viruses from that family, such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome – Coronavirus 2 (SARS-CoV-2), represent pathogens of great concern for public health. SARS-CoV-2 is the causative agent of COVID-19. SARS is characterized by an exacerbated inflammatory response, and the viral load is not associated with the worsening of the symptoms (Huang et al., 2020; Peiris et al., 2003). Death usually occurs due to severe atypical pneumonia (Song et al., 2019; Yin and Wunderink, 2018).

A recent study with 1099 patients with COVID-19 pneumonia in Wuhan showed that the most frequent clinical characteristics in the beginning of the disease are fever (88%), fatigue (38%), dry cough (67%), myalgias (14.9%), and dyspnea (18.7%). Pneumonia seems to be the most common and serious manifestation of the infection. In this group of patients, difficulty to breathe appeared after an average of five days of infection. The acute respiratory distress syndrome was present in 3.4% of the patients (Guan et al., 2020a,b).

Currently, there are no effective treatments available against COVID-19 and medical protocols involve: isolating the patient and providing treatment for those who display mild symptoms; or oxygen therapy/ventilator for those in a severe state. Alternative therapies have also been proposed and many results in clinical practice have shown that traditional Chinese medicine (TCM) plays a significant role in the treatment of COVID-19. For patients with mild and common symptoms, an early TCM intervention may result in the prevention from transforming into a severe state of the disease (Ren et al., 2020).

Precautions should be taken until some of the studies being performed can provide more reliable data regarding the efficiency of drugs that can effectively be used against COVID-19. Therefore, our goal is to review recent studies that were carried out by different authors on drugs suggested for the treatment of COVID-19 and their results, in order to synthesize the current available knowledge on the use of medical drugs for such treatment.

2. Drugs used in the treatment of COVID-19

Fig. 1 presents the mechanisms of action of the main drugs suggested for the treatment of COVID-19.

Adapted from Caly et al. (2020), Salvi and Patankar (2020), Fragakou et al. (2020).

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https://doi.org/10.1016/j.ejphar.2020.173467
Received 6 May 2020; Received in revised form 27 July 2020; Accepted 6 August 2020
Available online 8 August 2020
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2.1. Chloroquine and hydroxychloroquine

Malaria is a disease in which chloroquine has been used as the first-line treatment for several decades (Al Bari, 2015). Hydroxychloroquine is widely used in autoimmune diseases, such as lupus and rheumatoid arthritis (Touret and Lamballerie, 2020).

Some recent publications have pointed out that chloroquine could act against SARS-CoV-2. A study with more than 100 patients showed that the use of chloroquine seems to be effective, with a reduction in pneumonia aggravation, in the duration of the symptoms and in delayed viral clearance without relevant side effects. The therapeutic recommendation was of 500 mg of chloroquine twice a day in patients with severe COVID-19 pneumonia (Gao et al., 2020). Gautret et al. (2020) evaluated the role of chloroquine in respiratory viral load and observed a significant reduction in the viral load and a shorter average duration of treatment. The addition of Azithromycin to the treatment, concomitant with the use of hydroxychloroquine, was significantly more efficient in eliminating the virus (Gautret et al., 2020).

Studies suggest that the mechanism of action of chloroquine and hydroxychloroquine aims to impair or inhibit the pH-dependent viral replication stages (Rolain et al., 2007; Keyaerts et al., 2004; Colson et al., 2020), interfere in the post-translational modification of viral proteins (Savarino et al., 2001), or act on the immune system (Accapezzato et al., 2005).

The use of chloroquine/hydroxychloroquine in rheumatic diseases and in antimalarial prophylaxis showed a low incidence of adverse events and, in these cases, the most serious toxic effect is macular retinopathy, which depends on the cumulative dose and not the daily dose (Savarino et al., 2003). The use of chloroquine in mild to moderate overdose can result in nausea and vomiting, metabolic acidosis, hypokalemia, headache, neuropsychiatric side effects, and visual disturbances (e.g. blindness). In severe overdose, it can result in convulsions, cardiac arrhythmias, depressed myocardial contractility, shock, severe hypokalemia, and death through respiratory and circulatory collapse (Karalisa et al., 2020).

On June 17th, WHO reported that the evidence of efficacy and safety of hydroxychloroquine or chloroquine used in treatment of SARS-CoV-2 is limited and of very low certainty, as its administration was not related to a difference in overall mortality compared to standard care. Furthermore, its administration may result in more adverse events than standard care (WHO, 2020b).

2.2. Antivirals

Retrospective SARS data suggest that early treatment – within 1–2 days after hospital admission, for example – may be more effective than postponing therapy until organ failure occurs. This is consistent with data on influenza infection, which suggest a limited treatment window that occurs relatively early in the course of the disease.

2.2.1. Lopinavir/Ritonavir

This drug is commonly used to treat the human immunodeficiency virus (HIV). It is used in combination with other drugs to treat adults and children older than 14 days infected with HIV-1 (Su et al., 2019). The most frequent side effects observed are diarrhea, nausea, and vomiting and these effects are generally mild to moderate. Hyperlipidemia and glucose intolerance have also been observed in lopinavir/ritonavir recipients (Chandwani and Shuter, 2008).

Some studies report *in vitro* antiviral activity against the coronavirus associated with SARS when lopinavir is combined with ribavirin. A clinical study showed that the mortality rate of the group treated with that drug was lower than the control group. This study also revealed six deaths of patients treated with the conventional treatment. In the group that received the antiviral, only one patient had severe symptoms of hypoxia, but no deaths were reported. In addition, patients initially treated with lopinavir/ritonavir displayed a decreased viral load and an increased peripheral lymphocytes count (Chu et al., 2004).

However, another clinical study, with a total of 199 patients with SARS-CoV-2 infection confirmed in laboratory, treated 99 patients with lopinavir/ritonavir while 100 patients received standard treatment. The lopinavir/ritonavir combination was not effective when compared to the standard treatment. The mortality rate after 28 days was similar in both groups. When compared to the conventional treatment, no benefits were observed with the pharmacological use of these antivirals in adult

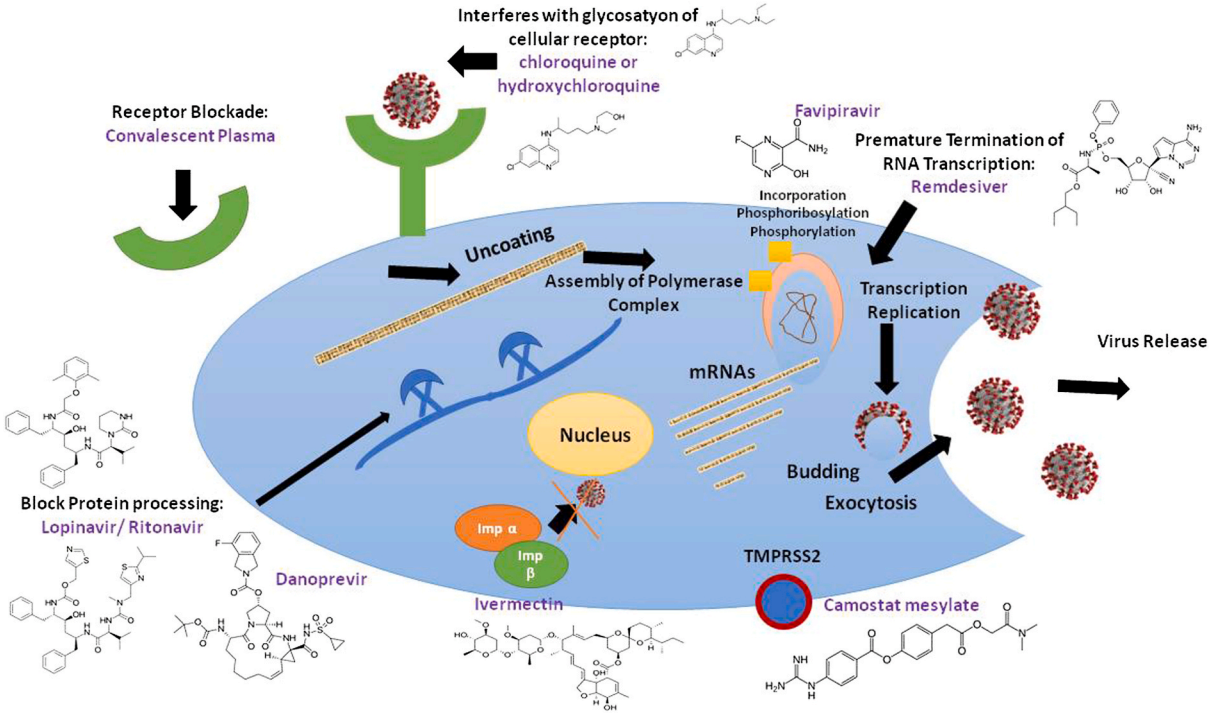

Fig. 1. Mechanisms of action of the main drugs.

patients hospitalized with COVID-19 in a serious condition (Cao et al., 2020).

Computational modelling designed to track possible drugs for the treatment of diseases is remarkably effective in terms of narrowing down the large number of possible molecules that may be used for such treatment. A modelling study involving anti-HIV drugs, specifically lopinavir/ritonavir, which would supposedly have an effect on the treatment of coronavirus pneumonia, was analyzed. The results were unsatisfactory, which implies that the drugs based on lopinavir and ritonavir may not be adequate for the treatment of SARS-CoV-2 infections. However, the results presented by these researchers are based on computer virtual screening. *In vivo* or *in vitro* experiments with those antivirals have not been carried out (Wu et al., 2020).

2.2.2. Danoprevir/Ritonavir

According to studies carried out thus far, about 5% of the COVID-19 cases become critical, and 50% of these result in death. For that reason, it is crucial to treat and prevent mild or moderate cases progressing to severe or critical states (Guan et al., 2020a,b).

Danoprevir is a potent inhibitor of the hepatitis C virus (HCV) protease. It was approved and has been commercialized since 2018 in China as a direct-acting antiviral agent. Its pharmacological availability is obtained orally. The results of a clinical assay performed with 140 patients showed that danoprevir, potentialized by ritonavir and interferon, produced a sustained virologic response (SVR12) rate of 97.1% after 12 weeks of treatment for the hepatitis C virus. These results show that the combination danoprevir/ritonavir is highly effective, safe, and well tolerated in HCV patients (Wei et al., 2019).

A similar treatment was tested in a clinical setting, and it revealed that the danoprevir/ritonavir therapy can suppress viral replication in less than a week and is effective in reducing ground-glass opacity (GGO) areas. Viral nucleic acids detected through nasal swabs become negative about 2–3 days after the beginning of the treatment with danoprevir/ritonavir. Thus, researchers believe that a successful treatment, performed for the first time using HCV protease inhibitor in three patients infected with COVID-19, may be effective to suppress viral replication and improve the health conditions of patients, especially for those with COVID-19 in a moderate state (Chen et al., 2020b).

Even though there are many promising studies regarding the mechanism of action and activity of protease inhibitors against SARS-CoVs, there are still not enough *in vitro* and *in vivo* studies against SARS-CoV-2 that can be used with confidence for COVID-19. Due to the lack of officially approved drugs for this condition, these studies are being used in an ad-hoc and compassionate manner based on case reports and previous experiences (Sisay, 2020).

2.2.3. Favipiravir

Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is an antiviral drug that selectively inhibits the RNA-dependent RNA polymerase of influenza virus. It also inhibits influenza strains resistant to current antiviral drugs, and shows a synergistic effect in combination with oseltamivir, thereby expanding influenza treatment options (Furuta et al., 2013).

Favipiravir may have potential antiviral action on SARS-CoV-2, which is an RNA virus. Cai et al. (2020) compared patients treated with Favipiravir with those treated with Lopinavir/Ritonavir and they found that the administration of Favipiravir showed better therapeutic responses to COVID-19 in terms of progression of viral clearance and disease. Clinical studies for comparison between Favipiravir and Arbidol were also carried out, and the researchers found that there was no clinical recovery rate among patients on day 7, but Favipiravir significantly improved the symptoms of pyrexia and cough and their adverse effects were mild and controllable. During the tests, some associated adverse effects were detected, including increased serum uric acid, psychiatric symptom reactions or digestive tract reactions, but most of these adverse reactions disappeared by the time the patients were discharged (Chen et al., 2020a).

2.2.4. Remdesivir

Remdesivir (GS-5734™) is an antiviral drug developed by Gilead Sciences initially developed to treat Ebola, but experimental tests are also being carried out to treat diseases such as MERS and COVID-19.

Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown *in vitro* activity against SARS-CoV-2 (Grein et al., 2020). Clinical studies conducted using this drug have shown an improvement in oxygen-support status in 68% of the patients. The study did not collect viral load data to confirm the antiviral effects of remdesivir or any association between initial viral load and viral suppression. Furthermore, the duration of remdesivir therapy was not entirely uniform, as with the clinical improvement the patients were allowed for leaving hospital. Further treatment with placebo will be carried out to verify the effectiveness of the treatment (Grein et al., 2020). Another study carried out with adult patients hospitalized with severe COVID-19 did not demonstrate significant clinical benefits. In this study, the most common adverse events in the remdesivir group were constipation, hypoalbuminemia, hypokalemia, anemia, thrombocytopenia, and increased total bilirubin (Wang et al., 2020).

2.3. Camostat mesilate (Foipan™) and Nafamostat mesilate (Buipel™)

Camostat mesylate is a synthetic proteolytic enzyme inhibitor for trypsin, plasmin, kallikrein, tissue kallikrein, and thrombin. It also shows activity in the treatment of pancreatitis and reflux esophagitis (Kwon et al., 2009). Nafamostat mesylate is also a synthetic serine protease inhibitor approved in Japan for the treatment of acute pancreatitis, disseminated intravascular coagulation and for anticoagulation in extracorporeal circulation (McKee et al., 2020). When used against dyspepsia associated with non-alcoholic mild pancreatic disease, it showed no severe adverse effects, indicating that it is a well-tolerated drug (Sai et al., 2010).

Studies carried out on rats have shown that camostat mesylate was effective is reducing death after a lethal infection by the SARS-CoV virus, with a survival rate of 60% (Zhou et al., 2015). Its suitability for the treatment of COVID-19 is still unclear, and it is not known which concentration of the compound is sufficient to control the viral spread (Hoffmann et al., 2020). Other drugs, such as Nafamostat mesylate, are still been tested (Hoffmann et al., 2020).

Clinical studies is now being conducted (NCT04353284) by Yale University with the intention of verifying whether Camostat mesylate can reduce the viral load of SARS-COV-2 at the onset of COVID-19 disease (ClinicalTrials.gov, 2020).

2.4. Ivermectin

Ivermectin belongs to the chemical group of avermectins, a semisynthetic microlide antibiotic that is isolated from *Streptomyces avermitilis*. It is widely used in large animals, for the treatment and control of parasitic infections caused by gastrointestinal and pulmonary nematodes, in berne infestations (myiasis), lice, and to assist in the treatment of scabies and ticks. In humans, ivermectin has been used as a prophylactic drug in the treatment of filariasis and has been used recently to treat scabies. It is a drug approved by the FDA and shows to be safe in the recommended dosages (200 μg/kg). Nonetheless, at dosages of 300 or 400 μg/kg, patients submitted to the treatment did not present any major clinical side effects other than mild itching (Ribeiro et al., 2001).

Ivermectin has also been studied due to its antiviral activity against a wide range of viruses *in vitro* (Wagstaff et al., 2012). It has been shown to inhibit the replication of HIV and also to limit retrovirus, adenovirus, and pseudorabies virus (PRV) infection, both *in vitro* and *in vivo*. However, no efficacy of this drug was observed against Zika virus (ZIKV) (Caly et al., 2012; Jans et al., 2019; Lv et al., 2018).

According to ongoing studies, the causative agent of COVID-19,

SARS-CoV-2, is an RNA virus. In order to test the action of ivermectin, Australian researchers infected cells with the virus and treated them with 5 μM ivermectin. They assessed virus replication after 24 h and observed a 93% decrease in the viral RNA in the supernatant. After 48 h, this effect was amplified, and a reduction of approximately 5000 times was observed in the viral RNA in the samples treated with ivermectin, compared to control samples. This result shows that the treatment with ivermectin may be very promising for *in vitro* samples. The researchers did not notice any ivermectin toxicity in the samples they tested (Caly et al., 2020).

In order to reduce viral load and prevent serious diseases and interpersonal transmission, researchers aim to have clinical tests approved so they can verify *in vivo* the antiviral capacity of that drug when it is administered in patients at the beginning of the infection (Caly et al., 2020).

However, another study (Momekov and Momekova, 2020) mentioned that the concentrations of ivermectin used in the aforementioned study are not feasible, as 5 μmol/l is 50 times higher than the levels used in medical practice and 17 times higher than the C_{max} seen in the literature (247.8 ng/ml). In that study, the authors also state that the suggestion made by the Australian researchers of inhibiting the virus through a single dose of the drug is inadequate because the cells are continually infected and the concentrations would not be maintained, even with excessive doses of the drug.

2.5. Dexamethasone

Corticosteroids have been extensively used in syndromes related to COVID-19, including SARS, MERS, severe influenza, and pneumonia. Clinical trials have been conducted with dexamethasone in the United Kingdom and the drug has been classified as the first steroid to prevent deaths from COVID-19. About 2100 patients received the drug in doses of 6 mg over 10 days and the death of a third of the patients who were receiving mechanical ventilation and a fifth of the patients who were receiving oxygen therapy was reduced. No effect was observed in the cases in which patients were not receiving respiratory support. The benefit in the use of dexamethasone when respiratory support is needed suggests that the disease is dominated by immunopathology in this phase, with the active replication of the virus playing a secondary role. It is also possible that an effect via mineralocorticoid receptor binding in the context of SARS-CoV-2 induced dysregulation of the renin-angiotensin system is presented. The advantages of dexamethasone are effective treatment for the sickest patients at a low cost, well-understood safety profile, and wide availability (Horby et al., 2020; Ledford, 2020).

2.6. Plasma

Convalescent plasma therapy is not a new idea; it was previously used for the treatment of the Machupo virus (Bolivian hemorrhagic fever), Junin virus (Argentinian hemorrhagic fever), Lassa fever and Ebola virus (Cheng et al., 2005). The use of immunoglobulin-rich convalescent plasma has shown beneficial effects in the treatment of infected mice (Ben-Nathan et al., 2003). The use of plasma for SARS has shown that, even with limitations, it has the capacity of carrying specific IgG and IgM antibodies against coronavirus, suppressing the progress of the infection (Cheng et al., 2005).

Clinical studies performed with five patients on mechanical ventilation, presenting severe respiratory failure and being monitored in an intensive care unit, report that the administration of convalescent plasma in patients, at an advanced stage of COVID-19, results in recovery after one week of use. However, these patients had a concomitant antiviral treatment with lopinavir/ritonavir and interferon. The use of convalescent plasma is believed to have contributed to the recovery of infected patients. In 1–12 days after the transfusion, body temperature normalization and stabilization of multiple organ failure were observed. In addition, during this period of 1–12 days, patients tested negative for SARS-CoV-2 in the airway mucosa (Shen et al., 2020).

In addition to the action of antibodies, there are other factors involved in the use of convalescent plasma. An *in vivo* study reported that antibody effects are not limited to eliminating the viruses, but also include preventing new infections and intensifying the regeneration of infected cells. Other components of the plasma may also have beneficial effects, such as the presence of coagulation factors in patients with hemorrhagic fevers (Cheng et al., 2005).

On the other hand, other aspects of the convalescent plasma should be noted. For instance, it varies from individual to individual depending on the type of antibody and its concentrations. Therefore, the plasma needs adjusting for the transfusion process. For this therapy to be effective, the creation of blood banks that store standardized and characterized frozen plasma is necessary so a wider population can benefit from it (Kraft et al., 2015).

Although researchers around the world agree that the use of convalescent plasma is a potential treatment for specific cases such as emerging infectious diseases and pandemics, the lack of clinical studies to put the treatment into practice is also evident (Chen et al., 2020c).

2.7. Anticoagulants

Anticoagulants are associated with the treatment of COVID-19, not with the purpose of reducing viral infection, but for the comfort of the patient in order to help other forms of treatment or to treat symptoms not related to the disease, such as those resulting from long periods of hospital stay.

Recent studies report that SARS-CoV-2 induce, in more severe cases, the production of a cascade of cytokines, which results in the activation of coagulation and, therefore, thrombotic phenomena (Dolhnikoff et al., 2020). The virus enters the respiratory epithelium causing a systematic aggression in the bronchi and alveoli which, due to this exposure, fosters a cascade of reactions to ensure local protection. With that, coagulation factors are produced in mass, resulting in a hypercoagulability state. This exacerbation does not eliminate the problem and triggers what is known as disseminated intravascular coagulation (DIC), which happens frequently in severe COVID-19 patients (Tang et al., 2020). Ten autopsies were performed in patients who died from COVID-19 in Brazil. The general pulmonary histological state observed was of exudative/-proliferative diffuse alveolar lesion with intense viral infection in the lung epithelium. In addition, a variable number of small fibrinous thrombi in small pulmonary arterioles, as well endothelial swelling and other indicators of the coagulation cascade were observed. In summary, these results are consistent with those of the DIC being associated with COVID-19, and this might help in the decision to use anticoagulants in cases in which this suggestion is supported (Dolhnikoff et al., 2020).

These researchers also recommend the use of heparin for patients displaying severe symptoms of COVID-19, since this drug has shown, in preliminary studies, the ability to reverse the clots formed in the microcirculation of the lungs and other parts of the body. Another goal of these researchers was to reduce the need for mechanical ventilation by administering the drug early (Dolhnikoff et al., 2020). The use of heparin in a clinical setting for 7 days or longer resulted in a decreased mortality in more severe cases, especially the ones with SIC score >4 or D-dimer > 6 fold of upper normal limit. For these reasons, the use of anticoagulants, by intensive care teams, for patients with severe COVID-19 has been recommended; however, its effectiveness has yet to be validated (Tang et al., 2020).

3. Conclusion

Based on some recent publications, we can observe that none of the suggested treatments are completely effective to eliminate COVID-19. Science still needs time to gather consistent information obtained through clinical trials to confirm what effectively works and the side effects involved, as well as drug dosage and possible drug combinations.

What we have at the moment are palliative pharmacological alternatives, or at most, drugs that assist in the treatment of the symptoms and complications presented by the disease during its progress. However, having healthy eating habits and adequate levels of vitamins D and B help the maintenance of the immune system, which is one of the many suggestions to prevent the disease.

Submission declaration

All authors have read and approved the submission of the manuscript; the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language. Vanessa Aparecida Marcolino Pitarelli, Ph.D, Tatiana Colombo Pimentel, Ph.D, and Carlos Eduardo Barão, Ph.D.

Declaration of competing interest

Author declares that has no conflict of interest.

Acknowledgements

The authors would like to express thanks to the Academic Publishing Advisory Center (*Centro de Assessoria de Publicação Acadêmica*) of the Universidade Federal do Paraná for their language support for this version of the manuscript.

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