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PERSPECTIVE ARTICLE

SARS-CoV-2: Recent Reports on Antiviral Therapies Based on Lopinavir/Ritonavir, Darunavir/Umifenovir, Hydroxychloroquine, Remdesivir, Favipiravir and other Drugs for the Treatment of the New Coronavirus

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Abstract: Here we report on the most recent updates on experimental drugs successfully employed in the treatment of the disease caused by SARS-CoV-2 coronavirus, also referred to as COVID-19 (COronaVIrus Disease-19). In particular, several cases of recovered patients have been reported after being treated with lopinavir/ritonavir [which is widely used to treat Human Immunodeficiency Virus (HIV) infection] in combination with the anti-flu drug oseltamivir. In addition, remdesivir, which has been previously administered to Ebola virus patients, has also proven effective in the U.S. against coronavirus, while antimalarial chloroquine and hydroxychloroquine, favipiravir and co-administered darunavir and umifenovir (in patient therapies) were also recently recorded as having anti-SARS-CoV-2 effects. Since the recoveries/deaths ratio in the last weeks significantly increased, especially in China, it is clear that the experimental antiviral therapy, together with the availability of intensive care unit beds in hospitals and rigorous government control measures, all play an important role in dealing with this virus. This also stresses the urgent need for the scientific community to devote its efforts to the development of other more specific antiviral strategies.

Keywords SARS-CoV-2, Coronavirus, COVID-19, antiviral drugs, hydroxychloroquine, remdesivir, favipiravir, lopinavir, ritonavir.

1. INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2, previously indicated as 2019-new coronavirus or 2019-nCoV) is a previously unknown pathogen responsible for COVID-19 (COronaVIrus Disease-19), a novel disease characterized, in several cases, by severe pneumonia, which emerged in Wuhan, Central China, in December 2019 [1]. As of March 26 2020, a total of 495086 cases of the new coronavirus SARS-CoV-2 infection were recorded worldwide, with the majority being recorded in mainland China, Italy, U.S., Spain and Germany, as reported on the real-time map developed by Prof. Gardner of Johns Hopkins University, Baltimore (US) [2, 3]. However, the problem has rapidly become global with numerous countries from Asia (including South Korea, Japan and many others), as well as America (U.S. mainly), Oceania, Africa and Europe (with cases from Italy, Spain, France, Germany, UK, Belgium and others) reporting numerous cases of infection [3]. This led the WHO (World Health Organization) to declare COVID-19 a pandemic on the 11th of March, 2020 [4]. SARS-CoV-2 is a betacoronavirus closely related to the bat-derived Severe Acute Respiratory Syndrome (SARS)-like coronaviruses [5], (showing an 88% genomic identity with two of them) and SARS-CoV-1 (about 79% iden-

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tity) [5]. The classification of SARS-CoV-2 into two major genotypes, Type I (further divided into Type IA and IB) and Type II, was recently proposed [6]. Type IA most resembles the ancestral SARS-CoV-2, while Type II, which probably evolved from Type I, is predominantly found in the current cases of infection [6]. During the SARS-CoV-1 outbreak in 2003, 349 people died in mainland China [7], while more than 3169 deaths caused by SARS-CoV-2 have been recorded to date (as of March 26, 2020) in the Hubei region (on a total of 22993 worldwide) [3]. At present, as of March 26, 2020, no vaccine or WHO-approved antiviral treatment for the new virus is available. Therefore, identifying drugs with antiviral activity against the new coronavirus is urgently needed and, to this aim, testing already existing antiviral drugs against SARS-CoV-2 is an obvious and timely approach. If one considers the number of fatal events (22993 to date) due to SARS-CoV-2 pneumonia when compared to the total of confirmed cases all over the world (495086 to date), a lethality of 4.6% can be estimated [3]. However, if the total number of 'concluded' cases (deaths + recovered cases) is taken into consideration, a ~16% of fatal events associated to SARS-CoV-2 can be estimated worldwide. However, because of limitations in testing, many cases of virus infection (especially in a less severe form) are not recorded. Obviously, this would lower the fatality rates significantly. Interestingly, in the last weeks, an encouraging trend has emerged mainly in China. In fact, as of February 4, 2020, a total of 20704 diagnosed cases, 427 deaths and 727 recovered patients were reported in the mapping tool [3]. Particularly in the Hubei region, from where the SARS-CoV-2 originated, there were more deaths than recoveries, as revealed by the above-cited real-time map [3]. After ~24 hours, those who had recovered from Hubei were 1.1 times greater in number than those who had died of the disease, while worldwide, the number of recovered/dead patients grew from 1.7 to 2.1. Interestingly, 5 days later (as of February 10, 2020), the same ratio was 2.1 for the Hubei region and 3.9 worldwide [3]. As of the 26th of March 2020, the recoveries/deaths ratio had further improved in China reaching a value of 19.3 for the Hubei province, which can be compared to a value of 5.2 when looking at the ratio for cases recorded worldwide. As can be noted, this worldwide ratio is lower than the value relative to China as it reflects the critical situation occurring in countries like Italy (with 74386 confirmed cases, 10361 recoveries, and 8165 deaths to date, as of March 26, 2020), as well as Iran and Spain where COVID-19 emerged more recently and is still not under control. Sadly, the ratio for recoveries/deaths in Italy is only ~1.3, *i.e.* lower than that which was recorded 1 and a half months ago in China (a country where, to date, COVID-19 appears to be almost under control). Thus, the data furnished by the real-time map suggest that in spite of the increasing number of confirmed SARS-CoV-2 infections, there are significantly more recoveries than fatalities worldwide and this is especially seen in countries like China and South Korea.

2. EXPERIMENTAL THERAPIES FOR COVID-19

In the last weeks, scientific reports and newspapers are reporting successful treatment of the new disease with different drugs, of which the most used are structurally represented below (Fig. **1**). One of the most common treatments available for SARS-CoV-2 consists of 'cocktail therapies' based on lopinavir/ritonavir, two protease inhibitors administered to HIV patients recently also proposed in scientific literature as potential drugs for the treatment of COVID-19 [8, 9], the binding of which to the SARS-CoV-1 protease was predicted *in silico* [10].

However, lopinavir/ritonavir was developed for inhibition of HIV protease, whose main difference with respect to the SARS-CoV-2 counterpart (3CL^{pro}) lies within the divergent spatial structure of the HIV aspartic protease when compared to 3CL^{pro} cysteine protease [11]. This difference in the structure of 3CL^{pro} and HIV protease would affect the inhibition efficiency of lopinavir/ritonavir and justifies a certain scepticism on the actual validity of this treatment for COVID-19 [11, 12].

As a matter of fact, the lopinavir/ritonavir cocktail, in combination with the anti-flu drug oseltamivir [13], led to a significant improvement in the health conditions of a severely-compromised 71-yrs old woman [14] in Thailand, one of the first countries out of China reporting SARS-CoV-2 cases [3]. The patient showed significant improvements only 12 hours after being administered the 3-drug treatment and remarkably, after 48 hours, was virus-free [14]. Besides preliminary encouraging reports like this, the results of randomized, controlled clinical trials are needed to evaluate the safety and efficacy of a therapy in hospitalized patients diagnosed with COVID-19 treated with a drug in comparison with controls who did not receive the same treatment. The lopinavir/ritonavir cocktail failed in a small study in China on COVID-19 patients [15] but WHO suggested the need for larger trials with a greater variety of patients [15]. Interestingly, oseltamivir is

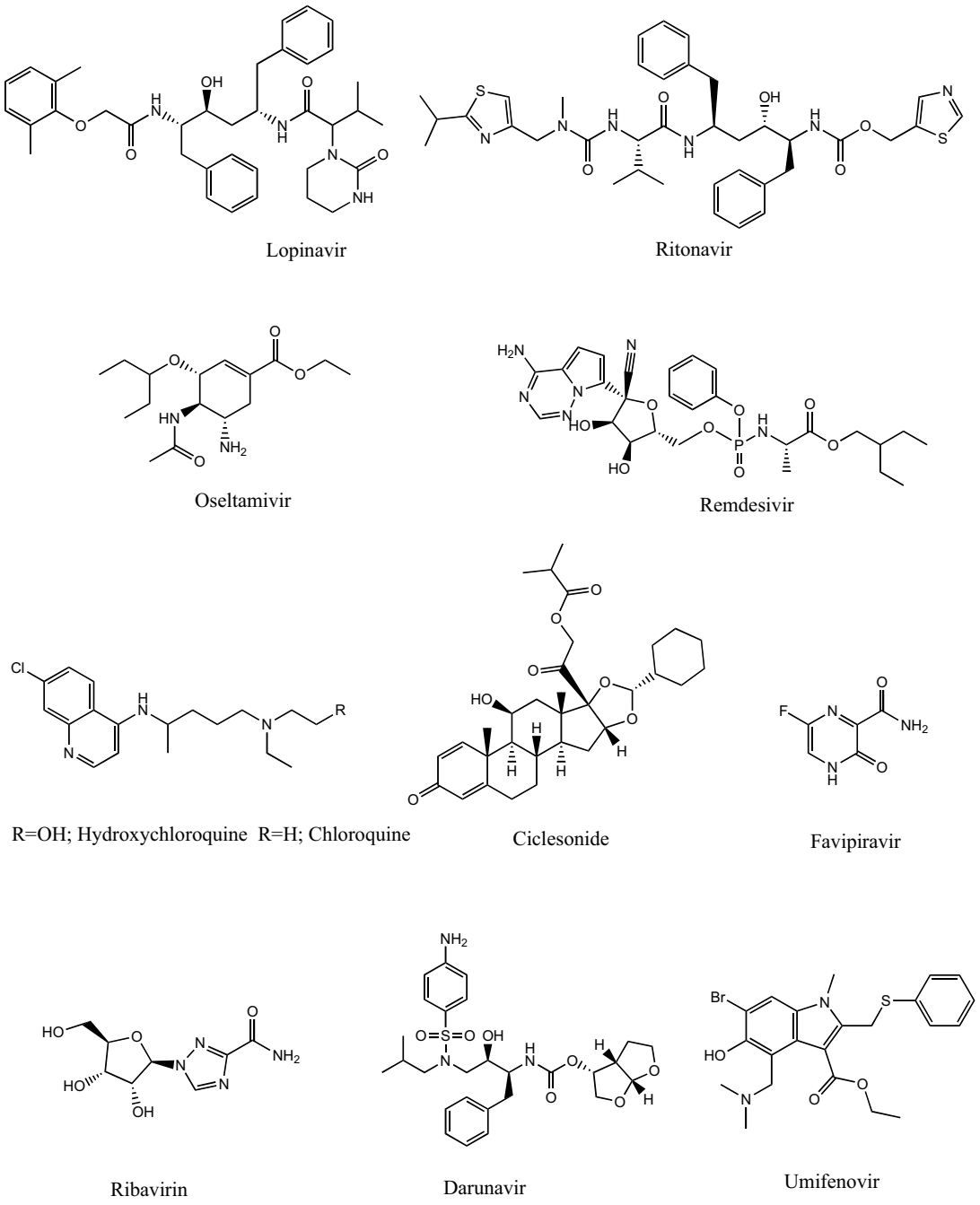

Fig. (1). Chemical structures of some of the drugs mentioned in this article.

also present in the flu drug mentioned by the physician who dealt with two patients who recovered from SARS-CoV-2 pneumonia in Australia at the end of January 2020 [16].

In the context of experimental anti-SARS-CoV-2 drugs, the *in vitro* studies of Wang *et al.* [17] revealed that remdesivir, a nucleotide analogue prodrug active against a wide array of RNA viruses and previously administered to West African Ebola virus patients [18], and the antimalarial chloroquine [19, 20] have significant effects in the control of SARS-CoV-2 infection. Particular importance is currently being attributed to another antimalarial drug, *i.e.* the chloroquine hydroxyl-derivative hydroxychloroquine (available as an antirheumatic drug under the name 'Plaquenil' [21]). This is due not only to its proposed *in vitro* anti-COVID-19 superiority over chloroquine [21, 22], but also to clues pointing towards its efficacy in the treatment of COVID-19 patients, which emerged in Japan [23]. Also worthy of note are the recent declarations made by Dr. Raoult from France, who reported significant improvements after 6 days of treatment with hy-

droxychloroquine (600 mg per day) on COVID-19 patients, even in combination with azithromycin [24]. This same drug, both affordable and commonly found worldwide, was included in some clinical trials which used it in high dosages [25] and is also mentioned in guidelines for COVID-19 therapy in Belgium (800 mg 1st day, 200 mg up to day 5) and Italy [26, 27]. Interestingly, the above-mentioned remdesivir, another promising drug for COVID-19 patients [28], was administered in the U.S. to a SARS-CoV-2-infected patient whose worsening clinical status prompted its compassionate use by his physicians [29]. The patient's pneumonia improved within 24 hours, with no obvious side effects [28, 29]. There are two clinical trials currently underway in China to evaluate the effects of parenteral remdesivir in patients with mild-to-moderate and severe COVID-19 [28]. However, it should be noted that remdesivir administration is not approved anywhere globally and its safety has not yet been fully demonstrated [30]. *In vitro* studies suggested Teicoplanin, an antibiotic used for Methicillin-Resistant *Staphylococcus aureus* (MRSA) infection [31], which is also active against MERS-CoV in the cell, as a potential treatment for COVID-19 patients [32]. The guanosine analogue ribavirin in combination with interferon-α [33], and ciclesonide, a glucocorticoid drug used to treat asthma, were also recommended for treating SARS-CoV-2 [23].

One of the most interesting drugs currently available against SARS-CoV-2 is favipiravir, an RNA-dependent RNA polymerase (RdRp) inhibitor administrated to Ebola virus-infected patients [34], approved in Japan for emerging influenza [34] and in China for the treatment of COVID-19 [33]. In fact, preliminary studies on 80 patients in China have demonstrated that favipiravir exerts an antiviral action more potent than lopinavir/ritonavir in the treatment of COVID-19, and that there are no serious adverse reactions reported for this drug [33].

Despite not being an antiviral agent, tocilizumab is currently used in Italy by Prof. Ascierto and colleagues for treating COVID-19 patients [35]. This monoclonal antibody was developed for the treatment of rheumatoid arthritis [36] and, being active against the Interleukin-6 Receptor (IL-6R), also blocks the IL-6-mediated immune response in COVID-19. China has approved the "off label" use of tocilizumab to treat pneumonia and the severe cytokine release syndrome induced by the immune system in coronavirus patients [37]. The drug has already been tested in Italy on 6 patients who experienced rapid improvement in their health only 24-48 hours after administration [35]. This certainly shows promise for its successful use on larger cohorts.

Finally, therapies involving umifenovir (Arbidol, a drug targeting the membrane fusion process of influenza viruses, [33, 38]) or darunavir in combination with umifenovir were suggested as possible strategies to combat the SARS-CoV-2 outbreak with different reported cases of patients recovering from the disease in China [39].

CONCLUSION

The increasing number of recovered patients and the recently recorded higher ratio of recoveries/fatalities seem to be in favour of the above-described approach of experimental therapies. These appear to have been used successfully by physicians in China, one of the countries with the largest number of infected patients to date, but also with the highest rate of recovery.

Overall, the above-cited reports suggest that pneumonia caused by SARS-CoV-2 can be treated with promising antiviral therapies, starting with pre-existing drugs for which no serious side effects have been noted. However, many of the reports of therapeutic effects are anecdotal and controlled clinical trials must be undertaken to actually show the efficacy of these drugs. Moreover, it can be posited that beginning early drug treatment of COVID-19 may prevent severe symptom development and lung damage making a difference in saving the lives of patients. Following these guidelines could increase the ratio of recoveries/deaths for this disease and will encourage the scientific community to focus its energies and resources on the ultimate goal of completely eradicating the new SARS-CoV-2 infection through specific antiviral approaches.

LIST OF ABBREVIATIONS

$3CL^{pro}$	=	Chymotrypsin-Like Protease
COVID-19	=	COronaVIrus Disease-19
HIV	=	Human Immunodeficiency Virus
IL-6R	=	Interleukin-6 Receptor
MERS-CoV	=	Middle East Respiratory Syndrome - Coronavirus
MRSA	=	Methicillin-Resistant *Staphylococcus aureus*
RdRp	=	RNA-dependent RNA polymerase
RNA	=	Ribonucleic Acid
SARS-CoV-2	=	Severe Acute Respiratory Syndrome Coronavirus 2

WHO = World Health Organization

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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