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# COVID-19: WELL-KNOWN DRUGS, NEW OPPORTUNITIES

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Up to now, coronavirus infection that causes an acute respiratory syndrome has been detected almost in all countries worldwide. Global spread of SARS-CoV-2 virus has become a world pandemic and there is no efficient and commonly accepted conventional therapy against COVID-19. Due to the existing emergency most drugs that can potentially be used to treat COVID-19 are allowed to be applied only basing on certain data probing their safety and efficiency against SARS-CoV. At present only Lopinavir/Ritonavir and Remdesivir are the only anti-virus drugs that are included into well-recognized management procedures for COVID-19 treatment; an acceptable alternative could probably be combined therapy that includes Hydroxychloroquine and Azithromycin. Given the existing situation, a lot of drugs that are usually used to treat other diseases are now being suggested as probable ways to treat COVID-19 taking into account all the available knowledge on pathophysiology of the infection.

In this review, basing on available data on how SARA-CoV-2 virus enters a cell and pathophysiological aspects of cytokine storm development, we have strived to highlight certain prospects related to applying anti-viral medications, anti-inflammatory and immune-suppressing drugs, vitamins and microelements that are widely used to treat and prevent various diseases. Most tested drugs as well as zinc preparations, and vitamins C and $D_3$ turned out to have not only immune-modulating but also anti-inflammatory properties; or either they were able to block ways for the virus to enter a cell or disrupt SARS-CoV-2 intracellular replication.

Having leant from previous experience in fighting against SARS and MERS, doctors have applied some existing drugs to treat COVID-19 infections in their clinical practices; clinical tests aimed at confirming their safety and efficiency in treating COVID-19 are still being performed at the moment. Although a lot of various treatment procedures have been suggested, it is necessary to perform specifically planned randomized clinical trials based on evidence-based medicine principles, if we want to determine the most suitable ones.

Key words: coronavirus, SARS-CoV-2, COVID-19, anti-viral medications, immune-modulating drugs, anti-inflammatory drugs, medications, clinical tests.

Starting from severe acute respiratory syndrome (SARS-CoV) in 2002 and Middle-East respiratory syndrome (MERS-CoV) in 2012 caused by coronaviruses, SARS-CoV-2 occurrence has become the third event when highly pathogenic and wide-scale coronavirus epidemic has spread throughout human population in the 21st century. On January 30, 2020 the World Health Organization (WHO) officially declared COVID-19 epidemic to be an internationally significant emergency in public healthcare [1, 2].

The epidemic outbreak was established to have been caused by a new virus that was different either from Middle-East respiratory syndrome coronavirus (MERS-CoV) or severe acute respiratory syndrome virus (SARS-CoV) [3, 4]. This virus belongs to RNA viruses' family called Coronaviridae, is probably recombinant and is carried by

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bats [5]. Recombination occurred in glycoprotein area on virus surface thorns where receptor of cell surface endocytosis was recognized, namely angiotensin-converting enzyme 2 (ACE2) [6, 7].

Accumulated data indicate that SARS-CoV-2 infection can cause acute respiratory syndrome that is greatly similar to a clinical picture usually occurring in case of pneumonia developed in people suffering from auto-immune diseases (that is, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis, and eosinophilic granulomatosis with poly-vasculitis), and auto-inflammatory diseases (for example, systemic idiopathic arthritis etc.) [8–10].

COVID-19 disease occurrence was related to full-blown anti-inflammatory status which was very similar to cytokine storm and involved producing and maintaining high contents of various cytokines including interleukins (IL)-1β, IL-1Rα, IL-2, IL-10, fibroblast growth factor (FGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP10), monocytes chemoattractant protein 1 (MCP1), macrophage anti-inflammatory protein 1 alpha (MIP1A), platelet-derived growth factor (PDGF), tumor necrosis factor alpha (TNFα), and vascular endothelium growth factor (VEGF) [11, 12]. Patients who are in critical state suffer from a drastic increase in contents of these factors, and IL-6 concentrations correlate with an increased in mortality [13, 14].

At present there are no standard procedures for treating COVID-19. Bearing in mind that the virus has a unique structure and the disease has different pathogenesis, it is necessary to develop COVID-19-specific treatment procedures, especially vaccines and antiviral medications. However, new vaccines development according to international standards will require not less than 18 months. As for new antiviral medications, it is still impossible to predict when they will be created and tested despite all promising possibilities available in the field. Given that, it is quite obvious that when the epidemic is at its peak, it is necessary to look for other solutions. Therefore, there has been an opinion that certain research works that could really make for finding these solutions should be aimed at developing and suggesting medications with their therapeutic properties being well-known from previous examinations, both traditional and non-traditional ones, that focused on studying other diseases with similar pathogenetic mechanisms. Bearing in mind that the epidemic is spreading rapidly and complications caused by it are rather severe, at present doctors who are treating infected patients need as much available therapeutic alternatives as it is only possible. This emergency the scientific society has to face when searching for ways to overcome COVID-19 pandemic calls for necessity to use medications that have not been properly approved as their usability for treating COVID-19 infections has only preliminary scientific justification.

When it comes to antiviral medications, experts have chosen to turn to previous experience gained in overcoming SARS and MERS; there are clinical tests being performed at the moment with their focus on estimating efficiency and safety of these existing medications when they are applied to treat COVID-19 [15]. In particular, bearing in mind that there are certain similarities between SARS-CoV-2 and other beta-coronavirus associated with such past epidemics as SARS-CoV and MERS-CoV experts took the same medications that had been used to treat them and yielded contradictory results (interferon, ribavirin, and lopinavir/ritonavir) and considered them as tool for treating COVID-19 [16, 17]. But it turned out that antiviral medications and systemic therapy with corticosteroids that was earlier applied in clinical practices, including neuraminidase inhibitors (oseltamivir, peramivir, zanamivir, etc.) as well as ganciclovir, acyclovir, and

ribavirin used to eliminate flu virus, were not efficient for treating COVID-19 and were not recommended [18, 19].

Such protease inhibitors as lopinavir and ritonavir that were used for treating human immunodeficiency virus (HIV), MERS-CoV, and SARS-CoV turned out to be quite efficient in treating COVID-19 in South Korea [20, 21].

Besides, remdesivir which is now being developed as an adenosine analogue for treating Ebola infection has recently been accepted as a promising antiviral medication against a wide range of RNA viruses; it has yielded positive preliminary results in treating SARS-CoV-2 infection [22]. Remdesivir has been shown to produce effects on virus RNA-dependent RNA polymerase (rdRp); it is able to efficiently avoid correction by virus exoribonuclease and prevents RNA virus transcription from completion [23]. Since its efficiency in treating patients with SARS-CoV-2 infection was estimated in March 2020, the medication has been recommended to be applied in a single oral dose equal to 200 mg on the 1st day with the subsequent maintaining doses equal to 100 mg taken once a day for 3–5 days [24].

Another nucleotide analogue used to destroy RdRp-dependent virus replication is called favipiravir; it has been approved on by research experts in several countries and has been proven to be able to make outcomes better for patients with COVID-19 [25]. As per preliminary results, favipiravir turned out to be more efficient in 80 cases than lopinavir/ritonavir and patients who took it didn't suffer from any significant adverse reactions [26].

Arbidol and arbidol mesylate have also been shown to produce significant inhibiting effects on SARS-CoV reproduction [27]. Basing on that, clinical experts combined western and Chinese treatment procedures, accordingly including lopinavir/ritonabir (Kaletra®), arbidol, and Shufeng Jiedu Capsule (SFJDC, traditional Chinese medicine); it allowed them to achieve significant improvement of symptoms related to COVID-19 pneumonia in Shanghai Clinical Center of China Public Healthcare [28]. At present, a wide range of antiviral medications are being tested as possible tools to overcome COVID-19 infection including nitazoxanide, nafamostat, darunavir, cobicistat, emtricitabine/tenofovir, etc. [29, 30].

Apart from using certain antiviral medications, experts have also suggested a lot of other medications usually applied to treat various diseases as probable tools to treat COVID-19; these suggestions result from considerable data being accumulated on the infection pathophysiology.

Glucocorticoids play a significant role in rheumatologic clinical practices and are widely used to treat such diseases as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), vasculitis, etc. due to their immune-depressing properties [31, 32]. However, high corticosteroid doses are closely connected with such adverse effects as secondary infections and virus resistance occurrence. In accordance with the Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment (the 7th edition)[1], in China only low and moderate corticosteroid doses can be potentially useful in therapy applied to treat seriously ill patients with COVID-19 pneumonia. The preliminary guide on clinical practices for treating COVID-19 published by the WHO does not recommend using corticosteroids excluding such clinical reasons as chronic lung disease exacerbation or septic shock [33].

Chloroquine and its derivative, hydroxychloroquine, are aminoquinoline com-

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[1] Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment (7th edition). Beijing: National Health and Family Planning Commission of China (NHPFC), 2020. Available at: http://kjfy.meetingchina.org/msite/news/show/cn/3337.html (13.05.2020).

plexes that are registered as medications for treating and preventing malaria and many other auto-immune diseases [34]. Chloroquine use as an anti-malaria medication is significantly limited nowadays to widely spread resistant malaria plasmodium, but hydroxychloroquine is now considered a vital component in primary treatment of RA and SLE due to its apparent immune-modulating effects [35].

Chloroquine can inhibit pH-dependent stages in replication of certain viruses including significant effects produced on SARS-CoV infectious agents. Besides, it has immune-modulating effects as it inhibits TNF-α and IL-6 production /release and it also acts as a new autophagy inhibitor that can prevent viruses from reproducing themselves [36]. Several research works revealed that chloroquine was able to block glycosilation of angiotensin-converting enzyme 2 (ACE-2) with an ability to inhibit SARS CoV-2 virus ability to enter cells. Preliminary results confirm that the medication can suppress COVID-19 pneumonia development thus improving a lung x-ray picture and reducing duration of the disease. Basing on this evidence, chloroquine and hydroxychloroquine were included into certain treatment procedures in China and Italy as well as in most other countries worldwide [37, 38].

However, experience gained via applying these medications in an actual epidemiologic situation has also revealed risks related to probable adverse effects [39, 40]. In rheumatology chloroquine and hydroxychloroquine are most widely prescribed and they are proven to have potential adverse effects such as retinopathy, cardiotoxicity, and myelotoxicity; these effects are a real threat for patients with rheumatoid arthritis and collagenosis in case the medications are taken for a long time [41]. In case there is acute COVID-19 infection, these medications can only be used for a very short period of time (5–20 days according to a recom-

mended treatment procedure) with probably an insignificant risk of adverse effects [37, 38]. Nevertheless, we should remember that such acute side effects as hyper-sensitivity and gastrointestinal intolerance require special attention, especially when it comes to patients with COVID-19 who are in critical condition.

Soon we expect to get access to results obtained via clinical tests with use of the 1st hydroxychloroquine dose equal to 400 mg taken in the 1st day and subsequent maintaining doses equal to 200 mg taken for the following 4 days; it will allow clarifying whether a theoretically strong effect can be produced by the medication on survival and recovery of patients with COVID-19 [42]. Until then, the medications remain basic ones in the current treatment procedures due to their impeccable safety profiles and huge experience on their use in clinical practices.

According to a recent research work, when azithromycin was added to a treatment strategy applied to treat a patient with severe COVID-19 (500 mg the 1st single dose, then 250 mg once a day for 2–5 days), it resulted in significant growth in hydoxychloroquine efficiency (200 mg thrice a day for 10 days) [43]. And at present several randomized clinical examinations are performed that involve use of such a combination to treat COVID-19 with different severity (NCT04321278, NCT04322396, NCT04322123, NCT04324463).

Non-steroid anti-inflammatory medications (NAFM) are easily available and are usually prescribed to treat pains, fever, and inflammations in case of many diseases, especially in rheumatology. Several years ago it was shown that a protein part in SARS-CoV thorn activated cyclooxigenase-2 expression, and naproxen turned out to have a counteracting effect; besides, it was detected that ibuprofen had inhibiting effects on ACE2 [44, 45]. It has been decided to examine naproxen efficiency when the medication is included into a standard treatment procedure for patients with COVID-19 who are in criti-

cal conditions; clinical tests are now at their $3^{rd}$ stage [46]. But at the same tine regular symptomatic use of NAFM is still not recommended as the primary variant in basic COVID-19 treatment due to such patients running higher risks of hospitalization, critical condition, and mortality which correlates with age and concomitant diseases, especially hypertension [47].

There has been a report recently on efficiency of tocilizumab, interleukin-6 inhibitor (humanized monoclonal antibody against IL-6 receptor which is used in rheumatoid arthritis treatment) for treating patients with severe COVID-19 pneumonia [48]. A randomized clinical examination aimed at estimating tocilizumab safety and efficiency in treating COVID-19 is still going on (ChiCTR2000029765). In China it was recommended to use tocilizumab as it provided an opportunity to treat patients with extensive and bilateral pneumonia or seriously ill patients with high IL-6 contents [48].

Another interesting anti-inflammatory medication is baricitinib, cytokine production inhibitor. It inhibits JAKkinase and is licensed to treat rheumatoid arthritis; reported efficiency and safety are quite satisfactory. Use of baricitinib in treating COVID-19 can bring good results as the medication acts against a wide range of cytokines. And finally, a minimal interaction between baricitinib and relevant CYP P-450 enzymes that metabolize it makes the medication a possible option to be included into treatment procedures in a combination with anti-viral medications such as lopinavir/ritonavir and remdesivir [49].

It is known that SARS-CoV-2 enters target cells via ACE2 receptor and trans-membrane protease, Serin 2 (TMPRSS2). And here TMPRSS2 inhibitors can prevent the virus from entering a cell due to blocking SARS-CoV-2 thorn protein [50]. Such effects are produced by camostat, a protease inhibitor used to treat chronic pancreatitis [51]. At present there is a randomized placebo-control examination focusing on use of this medication to treat COVID-19 (NCT04321096).

A vital task when it comes to treating COVID-19 is to block cytokine storm; very promising results were detected for dapson, a sulfone medication with anti-inflammatory effects; doxycycline, an antibiotic from tetracycline group; and promazien, a neuroleptic drug used in psychiatric practices [52–54]. There are randomized clinical examinations with participating out-patients with COVID-19 that involve use of these medications (NCT04322682) together with colchicine, anti-tumor and anti-inflammatory medication that inhibit cellular microchannel polymerization [53]. And finally, basing on data regarding produced effects, there is a clinical examination going on at the moment that focuses on efficiency of treatment with losartan for out-patients (NCT04311177) and hospitalized patients (NCT04312009) with COVID-19.

Vitamin D is known to control inborn and adaptive immunity and its deficiency is related to auto-immune reactions growth and increased susceptibility to infections; it can well play a significant role in decreasing COVID-19 risks [55, 56]. Since vitamin D deficiency is widely spread, especially among elderly people [57, 58] and it tends to grow in case sunshine is also in deficiency, it was probably not accidental that the $1^{st}$ SARS-Cov-2 outbreak occurred in winter season and involved high mortality among elderly people [59, 60]. In order to slow down virus replication and prevent anti-inflammatory cytokine production, there are several clinical examinations being performed on patients with COVD-19 at the moment; they involve use of vitamin D3 in a dose equal to 10.0 units per day during several weeks (NCT04334005, NCT04344041) [61].

Besides, basing on clinical results obtained in COVID-19 infection focus in China, experts made an assumption that taste and smell loss could be caused by zinc deficiency as such symptoms are quite typical

for this state [62, 63]. Since preliminary research has revealed that zinc produces inhibiting effects on coronavirus replication, it is assumed that if a person consumes zinc in a dose equal to 50 grams a day, it can provide certain protection against COVID-19 due to a body more efficiently resisting against the viral infection. The 1$^{st}$ clinical examination that involves intravenous zinc introduction into patients with COVID-19 is going on in Australia (ACTRN12620000454976). Besides, there are several clinical examinations being performed at the moment that involve use of zinc combined with other medications (that is, hydroxychloroquine, vitamin D, vitamin C) to treat COVID-19 (NCT04326725, NCT04351490, NCT04342728).

**Conclusions.** Therefore, we can conclude that the world is facing a new dangerous virus with higher pathogenicity than all the known infections. Over a few short months SARS-CoV-2 has spread throughout the world with menacing speed and is now threatening global and individual health and economic prosperity. At present there are no registered vaccines or standardized treatment procedures specifying certain medications and schemes for their use that are efficient against SARS-CoV-2. As it is a real emergency, most medications that can potentially treat COVID-19 are allowed to be used basing only on data on their safety and efficiency against SARS-CoV-2. At the moment only lopinavir/ritonavir and remdesivir are anti-viral medications that are included into serious treatment procedures for COVID-19 treatment; an acceptable alternative might be combined therapy with hydroxychloroquine and azithromycine. Given the existing situation and taking into account available data on the infection pathophysiology, experts have started to suggest many medications that are usually used to treat various diseases as possible treatment methods against COVID-19. We hope that clinical examinations involving use of these medications will allow obtaining high quality data; these data can be used to objectively estimate a probable therapy aimed at both treating and preventing this disease that causes a global emergency worldwide. Enhanced international cooperation and clinical examinations performed on a global level with a great number of patients participating in them should become a way for achieving valid and ultimate results.

**Conflict of interests.** The authors declare there is no any conflict of interests.

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