Review Article

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Therapeutic agents currently employed against Covid-19: an effort to control the pandemic

[Covid-19'a Karşı Kullanılan Terapötik Ajanlar: Pandemi Kontrolü İçin Bir Çalışma]

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Abstract: The disease caused by the new coronavirus (COVID-19) is characterized by fever and cough, in addition to affecting the lower respiratory tract and being associated with age, comorbidities and a weakened immune system. Lymphopenias occur in severe cases and an excessive production of inflammatory cytokines, which would explain the role of the hyperinflammatory response in the pathogenesis of COVID-19. In the absence of treatment for this virus, there is an urgent need to find alternative methods to control the spread of the disease, so we have conducted an online search for all treatment options related to coronavirus infections, as well as some infections due to viruses, general treatments, specific coronavirus treatments and antiviral treatments should be useful in the fight against COVID-19, the therapeutic agents evaluated included chloroquine/hydroxychloroquine, lopinavir/ritonavir, tocilizumab, ribavirin, interferons, nelfinavir, ivermectin, monoclonal antibodies and convalescent plasma.

Keywords: coronavirus; COVID-19; pandemic; SARS-CoV-2; therapeutic agents.

Öz: Yeni koronavirüsün (COVID-19) neden olduğu hastalık, alt solunum yolunu etkilemesine ve yaş, komorbiditeler ve zayıflamış bağışıklık sistemi ile ilişkili olmasının yanı sıra ateş ve öksürük ile karakterizedir. Lenfopeniler şiddetli vakalarda ortaya çıkar ve aşırı inflamatuvar sitokin üretimi, COVID-19'un patogeneğinde hiperinflamatuvar yanıt rolünü açıklar. Bu virüs için tedavi olmadığında, hastalığın yayılmasını kontrol etmek için alternatif yöntemler bulmaya acil ihtiyaç vardır, bu nedenle koronavirüs enfeksiyonlarıyla ilgili tüm tedavi seçenekleri ve virüslere bağlı bazı enfeksiyonlar için çevrimiçi bir araştırma yaptık. COVID-19 ile mücadelede genel tedaviler, spesifik koronavirüs tedavileri ve antiviral tedaviler yararlı olmalıdır; değerlendirilen terapötik ajanlar arasında klorokin / hidroksiklorokin, lopinavir/ritonavir, tocilizumab, rivabirin, interferonlar, nelfinavir, ivermektin, monoklonal antikorlar ve iyileşen plazma yer almaktadır.

Anahtar Kelimeler: COVID-19; Koronavirüs; Pandemi; SARS-CoV-2; Terapötik ajanlar.

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Introduction

In late 2019, the world underwent the start of a new pandemic caused by the so-called SARS-CoV-2 virus, referring to the clinical state caused by the new coronavirus as COVID-19 [1–5], which in its severe form leads to massive alveolar damage and progressive respiratory failure [6]. The incubation period for SARS-CoV-2 is five days on average [7], similar to that of SARS-CoV-1 causing the

epidemiological outbreak in 2003 [8], but with greater impact than that of H1N1 influenza from the year 2009 [9]. It is a positive single-stranded RNA virus, with a molecular weight of 27–32 kb, in which non-structural proteins are encoded, such as: helicases, proteases and RNA polymerases; in addition to structural, membrane (M), envelope (E), nucleocapsid (N) and spike protein (S). Protein S is a glycosylated protein that forms the homotrimeric tips on the surface of the viral particle, it is made up of two subunits: S1 and S2, which are cleaved within the endocytic vesicles during virus entry [10]. Protein M is primarily responsible for its shape and most abundant in viral structure, while E is found in small amounts and is responsible for the release of viral particles from host cells. Both proteins orchestrate the virus assembly and the formation of mature viral envelopes [11]. Protein N is found in the nucleus interacting with the viral RNA and giving shape to the nucleocapsid, being necessary for the packaging of the viral RNA during its assembly [12]. SARS-CoV-2 uses the spike protein to infect epithelial cells of the lung and intestine through a membrane receptor protein, called angiotensin-converting enzyme 2 (ACE2), very similar to the SARS-CoV-1 virus but different from MERS-CoV using the DDP4 receptor (dipeptidyl peptidase-4) [1, 13–15]. The SARS-CoV-2 genome is 79.5% similar to SARS-CoV-1 [16], presenting a peak that diverges in the receptor binding domain (RBD), so it would not efficiently bind to the human angiotensin-converting enzyme 2 (ACE2). The SARS-CoV-2 genotypes of subjects from different provinces of China have been analyzed with positive results for the disease and it was found that the virus had mutated in several of them, despite the degree of diversification of the SARS-CoV-2 is less than avian influenza (H7N9) [17]. Other works have analyzed the genomes of SARS-CoV-2 samples and found two predominant evolutionary types, type L (70%) and type S (30%). Type L strains are derived from type S, and are evolutionarily more aggressive, being more contagious [18]. Non-structural proteins and structural protein (S) have been the main therapeutic target of SARS-CoV and MERS-CoV [13]. In addition to the above, SARS-CoV-2 has a hemagglutinin esterase (HE), which is a surface protein of some coronaviruses, hemagglutinin binds to sialic acid residues in the plasma membrane of the host cell and the esterase hydrolyzes acetyl groups. The characteristics of HE could enhance the entrance to host cells and the pathogenesis of coronaviruses [19]. For the virus to enter host cells, the RBD of the S1 subunit of the S protein is required to act as a mediator to bind the virus to cell receptors, while the S2 subunit is the mediator of fusion events between the viral surface and cell membrane [20]. The ACE2 receptor protein is present in epithelial cells of

the ileum (30%), myocardium (7.5%), esophagus (>1%), proximal kidney tubules (4%) and urothelial cells of the bladder (2.4%), all of them being organs with a high risk of infection [21]. Symptoms generally appear 2–14 days after viral exposure, including fever, cough, shortness of breath, and pneumonia, severe cases show respiratory, liver, gastrointestinal, and neurologic complications that can lead to mortality, transmission of COVID-19 is human to human by respiratory droplets or by direct contact with infected subjects [22–25]. Based on the above, the objective of this review is to provide current and relevant information on the efficacy and safety of potentially therapeutic agents used against SARS-CoV-2.

Therapeutic agents used against infection

We can say that humans are not prepared to face this virus and therefore there is no proven treatment, preventing infection is the first and most important strategy to follow, which is achieved by isolating the case [26]. There are no studies on the effectiveness of the use of masks and hand hygiene to reduce the spread of SARS-CoV-2; However, there is evidence of this in other viral diseases such as influenza, in which the use of masks and hand hygiene decreased the transmission of the infection by 67% [27] and up to six times the value of the infection if it is that surgical masks are used [28]. Therefore, the patient with SARS-CoV-2 is sent to his home in order to isolate him until he recovers and is not a source of infection. During this period, temperature and vital functions should be controlled using antipyretics and symptoms if necessary. If the patient deteriorates, he should be transferred to a hospital where he will receive oxygen if his saturation is less than 90% or, in the case of pregnant women, if it is less than 92%. If necessary, you will enter the Intensive Care Unit (ICU) and, if required, you will be put on mechanical ventilation (MV). This MV begins, as far as possible, with the non-invasive form (NI), and if the patient does not tolerate it or has refractory respiratory failure, with invasive MV. Protection strategies such as low tidal volumes and pronation should be followed during MV. If the MV does not evolve well, if the resource is available, extracorporeal membrane oxygenation (ECMO) can be provided. There is no evidence from large controlled studies that the effective action of any medication has been demonstrated in subjects with SARS-CoV-2. Being a viral disease, it has been considered to use successful treatments in other viruses, such as those effective in AIDS, recommending Lopinavir/Ritonavir for 14 days [29], below we will discuss some of them.

Lopinavir (LPV)/ritonavir (RTV)

The combination of LPV with RTV is widely used as a protease inhibitor in the treatment of HIV infection. LPV is generally combined with RTV to increase the half-life of LPV by inhibiting cytochrome P450 [30, 31]. The CDC and WHO Clinical Practice Guidelines (CPG) do not contain specific recommendations regarding the use of LPV/RTV in cases of COVID-19. Chu (2004) demonstrated that the use of LPV/RTV with Ribavirin in the treatment of SARS was associated with a better result [32]. Kim (2016) reported on a successful case of MERS-CoV disease treated with triple combination therapy LPV/RTV, Ribavirin and IFN-alpha 2a in South Korea, regarding COVID-19, triple combination therapy of Kim should be considered as an option in the early stage of illness [33]. However, current data mention that WHO accepted the recommendation of the Solidarity Trial International Steering Committee to discontinue the hydroxychloroquine and lopinavir/ritonavir arms of the trial. The Solidarity Trial was established by the WHO to find an effective COVID-19 treatment for hospitalized patients. The results of these interim trials show that hydroxychloroquine and lopinavir/ritonavir produce little or no reduction in mortality for hospitalized COVID-19 patients compared to standard care. This decision applies only to the conduct of the Solidarity trial in hospitalized patients and does not affect the possible evaluation in other studies of hydroxychloroquine or lopinavir/ritonavir in non-hospitalized patients or as pre- or post-exposure prophylaxis for COVID-19 [5].

Remdesivir (RDV)

RDV, an adenosine analog, is a promising antiviral in RNA viruses (including SARS/MERS-CoV-5), 100% protection against Ebola was observed in non-human primate models [34]. RDV has been reported to inhibit human and zoonotic coronavirus *in vitro* and to restrict SARS-CoV *in vivo*. The antiviral activity of RDV together with IFN-beta was shown to be superior to the results obtained with LPV/RTV-IFN-beta against MERS-CoV *in vitro* and *in vivo*. RDV can improve lung function and reduce viral loads in the lungs of mice, a first case infected with COVID-19 was reported in the United States and the use of RDV was administered when the patient's clinical condition worsened. Therefore, the use of RDV with IFN-beta could be a better option for the treatment of COVID-19 compared to that of the triple combination of LPV/RTV-IFN-beta. Although still, controlled trials are needed to determine the safety and efficacy of RDV [35, 36].

Ribavirin

Ribavirin, a broad-spectrum antiviral agent, is commonly used to treat hepatitis C. During the SARS outbreak, ribavirin was widely used in most cases with or without concomitant use of steroids in Hong Kong [37]. Morgenstern (2005), had reported that ribavirin and beta interferon synergistically inhibited the replication of the SARS-associated coronavirus in animal and human cell lines. In view of adverse reactions and lack of efficacy *in vitro*, the use of ribavirin should be seriously considered for the treatment of COVID-19, even in combination with other antiviral drugs [38].

Tocilizumab

It has been used in subjects with COVID-19 in a small series of cases collected retrospectively by Xiaoling (2020), where 21 subjects with COVID-19 pneumonia in serious or critical condition (with alterations in the pulmonary tomography images and which required oxygen therapy) received conventional treatment and a 400 mg dose of tocilizumab. The authors report an average length of hospital stay of 13.5 days, after which only two subjects remained hospitalized. Additionally, an improvement in symptoms, hypoxemia and tomography images was described; adverse events have not been reported [39].

Nelfinavir

Nelfinavir is a selective protease inhibitor for HIV, during post-translational processing of HIV propeptides, the combination therapies became a standard for the treatment of HIV infections. The reasons for using combinations rather than single antiviral are better efficacy, decreased toxicity and the prevention of resistance emergence. The combinations of nelfinavir with salinomycin, amodiaquine, obatoclox, emetine or homoharringtonine were synergistic against SARS-CoV-2 in Vero-E6 cells. According to the available pharmacological data for these drugs, the most potent combination could be a combination of orally available nelfinavir and amodiaquine. This was also the combination that exhibited the highest synergy of all the drug combinations tested, the amodiaquine and nelfinavir combination could result in better efficacy and decreased toxicity for the treatment of SARS-CoV-2 and perhaps other viral infections [40]. Yamamoto (2004) mentions that nelfinavir could strongly inhibit the replication of the SARS coronavirus (SARS-CoV), thus becoming an option for the treatment of COVID-19 [41].

Ivermectin

Ivermectin is an antiparasitic approved by the United States Food and Drug Administration (FDA) and considered in the WHO list of essential drugs, it has antiviral action due to its inhibitory activity on nuclear transport. Ivermectin exerts broad-spectrum antiviral activity against several animal and human viruses, including both RNA and DNA viruses. The combination therapy using hydroxychloroquine and ivermectin may exert a synergistic inhibitory effect on SARS-CoV-2. In this combination, hydroxychloroquine acts by inhibiting the entry of SARS-CoV-2 into the host cells, whereas ivermectin further enhances the antiviral activity by inhibiting viral replication [42]. The antiviral potential of ivermectin against various viruses is mediated via the targeting of the following: importin α/β -mediated nuclear transport of HIV-1 integrase and NS5 polymerase; NS3 helicase; nuclear import of UL42; and nuclear localization signal mediated nuclear import of Cap. As SARS-CoV-2 is an RNA virus, the antiviral activity of ivermectin may be mediated through the inhibition of importin α/β -mediated nuclear transport of viral proteins. The clinical efficacy and utility of ivermectin in SARS-CoV-2-infected patients are unpredictable at this stage, as dealing with a completely novel virus. In cell culture, a single dose reduces SARS-CoV-2 RNA by about 5,000 times 48 h after administration [43, 44].

Interferons

The so-called interferons (IFN) are: IFN alpha, beta, gamma, and other subtypes [45]. IFN is an alternative to the treatment of COVID-19 [21, 46], since it was tested *in vitro* in trials with MERS and SARS giving good results [47, 48], however, Chan (2020), based on *in vitro* studies conducted in 2004, I indicate that the use of IFN is not recommended for subjects with COVID-19 and its use is only experimental. Clinical case studies show preliminary results, so there is no scientific evidence to support a recommendation in favor of IFN as an alternative treatment for subjects with COVID-19, results from randomized clinical trials are required to know both its efficacy and safety in subjects with COVID-19 [49].

Chloroquine and hydroxychloroquine

Chloroquine is a low-cost drug used for more than 70 years against malaria and for its anti-inflammatory properties in

rheumatic diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), it has shown superiority over control treatment in SARS-CoV-2 in subjects with pneumonia, which has improved radiographic images, has favored the disappearance of the virus and has shortened the course of the disease, without serious adverse reactions [50]. Chloroquine (CLQ), a well-known antimalarial drug, has shown apparent efficacy in the treatment of COVID-19-associated pneumonia in recent clinical studies [50]. However, the mechanism of action of CLQ against SARS-CoV-2 is unclear as the drug appears to exert a wide range of possible antiviral effects [51]. Therefore, although CLQ is classically considered an inhibitor of endocytic pathways through elevation of endosome pH [52], its detailed molecular mechanism of action as an antiviral compound remains unclear. CLQ has been shown to interfere with the terminal glycosylation of angiotensin converting enzyme-2 (ACE-2) [53], which acts as a plasma membrane receptor for both SARS-CoV [54] and SARS-CoV-2 [55], and CLQ could act at several steps in the replication cycle of coronavirus [53]. These data suggest the interesting and largely unexplored possibility that CLQ could prevent viral binding through a direct effect on host cell surface molecules. An important characteristic of human coronaviruses is that, in addition to their protein membrane receptor, they also depend on glycoproteins and gangliosides that contain sialic acid that act as primary binding factors throughout the respiratory tract [54–57]. Given the global health emergency, drug reuse is obviously the option of choice. However, a considerable amount of time could be saved by *in-silico* testing to determine the ability of any potential anti-SARS-CoV-2 to disrupt the interaction of protein S with the host cell membrane. Applied to both RBD-ACE-2 and NTD-ganglioside interactions, this molecular modeling method will help to select those drugs that are likely to interfere with the initial binding of virus particles to the respiratory tract surface epithelium [58]. It is worth mentioning that in mid-June 2020, the WHO announced that the hydroxychloroquine (HCQ) arm of the Solidarity Trial would be suspended to find an effective treatment against COVID-19, as recent results showed that hydroxychloroquine does not reduce mortality in hospitalized patients with COVID-19, compared to standard care [5].

Monoclonal antibodies (MNA)

Neutralizing MNAs are potential therapeutic tools that could be specifically directed to the receptor binding domain (RBD) of protein S or also to the ACE2 receptor

protein in such a way that in both cases viral entry would be blocked [59]. The structure of the interaction sites between the ectodomain of the SARS-CoV-2 protein S and the MNAs have already been obtained by bioinformatics (PyMOL) [1]. Eleven MNAs investigated in SARS may be useful for SARS-CoV-2 which have been evaluated *in vitro* and *in vivo*. A cocktail of these MNAs is suggested to counteract possible antigenic changes in the virus [1].

Convalescent plasma

Convalescent plasma (PC) is a passive immunization strategy that has been used in the prevention and treatment of infectious diseases [60]. PC is obtained by apheresis in survivors with previous infections caused by pathogens of interest in the that antibodies against the causative agent of the disease are developed, aiming to neutralize the pathogen for its eradication [61]. Due to its rapid availability, PC has been considered as an emergency intervention in several pandemics, including Spanish influenza, SARS-CoV, West Nile virus and, more recently, Ebola virus [62–66]. PC administered early after the onset of symptoms showed a reduction in mortality compared to placebo or no treatment in severe acute respiratory infections of viral etiology such as influenza and SARSCoV, however, a similar response was not observed in the disease due to Ebola virus [67]. During apheresis, in addition to neutralizing antibodies (NAb), other proteins such as anti-inflammatory cytokines, clotting factors, natural antibodies, defensins, pentraxins, and other undefined proteins are obtained from donors [68]. In this sense, the transfusion of PC to infected patients can provide additional benefits such as immunomodulation through the improvement of the severe inflammatory response [69]. The latter could be the case of COVID-19 in which an overactivation of the immune system can come with systemic hyperinflammation driven by IL-1 β , IL-2, IL-6, IL-17, IL-8, TNF α and CCL2, this inflammatory reaction can perpetuate lung damage involving fibrosis and reduced lung capacity [70, 71].

Two trials have been made available in subjects treated with convalescent anti-SARS-CoV-2 plasma (PC). The first corresponds to a communication from five critically ill patients connected to an MV [72]. After the PC transfusion, three patients could be removed from the MV; improvement was also observed in laboratory and clinical parameters, such as virus clearance, better oxygenation, and decreased inflammatory biomarkers. The second is a non-peer review trial based on 10 patients with severe COVID-19 pneumonia. Its main objective was to assess the feasibility and safety of

the transfusion of PC. Only one event of facial redness was reported in one patient, while the rest of the patients received the transfusion without major mishaps. The reported clinical outcomes were modest and not very informative, they were only described until the third day after the transfusion, and although two patients out of three were withdrawn from MV, the majority remained with the same oxygen requirement [73]. Using PC is a safe and potentially effective strategy for treating emerging and reemerging pathogens, especially in those settings without proven antiviral agents or vaccines. The possible antiviral and immunomodulatory effects of PC are currently being evaluated in COVID-19, however more clinical trials are required.

Others

Some others may be: Papain-linked protease inhibitors (PLP) [74], S-ECA2 protein inhibitors or blockers [75], water-soluble vitamins [76–78], fat-soluble vitamins [79, 80], flavonoids [74] and omega-3 [81].

Final considerations

As final considerations we can say that, currently, in the absence of a drug supported by adequate studies in any part of the world, routine management of patients, specific treatments against coronavirus and antivirals may be useful to combat COVID-19, on the other hand, the WHO has started the so-called ECA SOLIDARITY, is a prospective study that seeks a comparison between the efficacy and safety of routine management, in addition to routine management associated with RDV, chloroquine or hydroxychloroquine, LPV/RTV alone and LPV/RTV plus IFN-beta, in order to establish treatment with the best risk-benefit balance for patients with COVID-19, all in which is a vaccine that works effectively against the virus.

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