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Options of Treatment in SARS-CoV-2 Infections

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Abstract

English:

Starting December 2019, in China, the SARS-CoV-2 infection became a local health issue, but its high infectiveness quickly turned it into a pandemic, to be declared an epidemiological emergency of international concern less than two months from identifying the first cases. Despite tremendous efforts aimed at discovering new drug classes that would slow down or stop the evolution of the COVID-19 disease and curb the number of severe cases and related complications, there is no specific antiviral treatment to date. The only efficient measure proved to be the prophylaxis, through vaccination.

Keywords

SARS-CoV-2 • COVID-19 • pandemics

Optiuni de tratament in infectia SARS COV 2

Rezumat

Romanian:

Incepand cu decembrie 2019 in China, infectia cu virusul SARS-CoV-2 a devenit initial o problema de sanatate locala, insa contagiozitatea crescuta a determinat in timp scurt producerea unei pandemii, fiind declarata urgenta epidemiologica de importanta internationala la mai putin de 2 luni de la identificarea primelor cazuri. Chiar daca s-au facut eforturi mari pentru descoperirea unor clase de medicamente care sa incetineasca sau sa opreasca evolutia bolii COVID-19 si sa scada numarul cazurilor severe si a complicatiilor produse de aceasta, pana la acest moment nu exista un tratament antiviral specific. Singura masura eficienta s-a dovedit a fi profilaxia, realizata prin vaccinare.

Cuvinte-cheie

SARS-CoV-2 • COVID-19 • pandemie

Introduction

The first 4 cases of people infected with SARS-CoV-2 occurred in Wuhan, China, on 29 December 2019 (1). The genomic sequence of the virus was identified and made public only by 10 January 2020, thus helping develop molecular diagnostic methods (2). The virus was named SARS-CoV-2 on 11 February 2020. WHO (World Health Organization) officially declared the pandemic caused by this virus, called COVID-19, an epidemiological emergency of international concern on 30 January 2020 (3). The COVID-19 pandemic was declared on 11 March 2020, less than 3 months from the emergence of the first cases (4).

By the 1st of October 2021, 238 079 649 cases of SARS-CoV-2 infections and 4 859 208 related deaths were reported worldwide. In Romania, to this date, there were 1 332 221 cases of infections and 38,927 deaths caused by this infection (5). The first case was confirmed in Romania on 26 February 2020, namely a young male aged 25 years who was a contact of an Italian citizen that had visited the country in 18-22 February and was later confirmed in Italy on 25 February 2020 (6).

The SARS-CoV-2 infection can stay asymptomatic or become symptomatic in time. Some asymptomatic cases were associated with CT exam modifications, such as ground-glass opacities (7). A meta-analysis on 24 410 adults from 9 countries concluded that the main symptoms are fever, cough and fatigue (8). The main symptoms found in hospitalized patients were fever, cough and dyspnea, followed by myalgias, headaches,

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anosmia or ageusia (9). The infection may worsen with dyspnea, acute respiratory failure, to critical forms with septic shock, need for mechanical ventilation, multiple organ failure and admission to the intensive care unit (10).
The high infectiveness of the virus, the economic impact of the pandemic, as well as the pressure of patients with severe forms of infection on the healthcare system and particularly on the intensive care sector worldwide created the need to identify an optimal treatment against the SARS-CoV2 infection.

Therapeutic options for COVID-19

NIH (National Institutes of Health) and WHO (World Health Organization) prepared guidelines for the management of the SARS-COV-2 infection with current data on therapeutic options. In the initial stage of the infection, the symptoms are a consequence of viral replication, thus requiring the initiation of the antiviral treatment, while the following period of clinical evolution, where the immune and inflammatory response leads to tissue destruction, requires immunosuppressive and immunomodulatory therapies that should be used in the late stages of the disease. In mild to moderate forms of the disease, posing no risk of progression of the disease, the symptomatic therapy is recommended.
The therapeutic classes used in the SARS-COV-2 infection are as follows:

- antiviral drugs – Remdesivir, Chloroquine and Hydroxychloroquine, Azithromycin, Ivermectin, Lopinavir-Ritonavir and other HIV Protease Inhibitors;
- Anti-SARS-CoV-2 antibodies – monoclonal antibodies, convalescent plasma, specific immunoglobulins;
- immunomodulators – colchicine, corticosteroids, Fluvoxamine, non-SARS-COV-2 specific immunoglobulins, Interferons (Alfa and Beta), Interleukin-1 Inhibitors, Interleukin-6 Inhibitors, Kinase Inhibitors (Baricitinib);
- Antithrombotic and anticoagulant therapy;
- Supplements – vitamin C, vitamin D, Zinc (11).

Remdesivir was proposed for the treatment of the SARS-CoV-2 infection as antiviral treatment due to the numerous good results it has demonstrated in vitro, proving to be active against Hepatitis B virus, Ebola, respiratory syncytial virus and SARS-CoV. Remdesivir has proven efficient in a rhesus macaque that was infected with Ebola and developed the disease, showing a suppression of viral multiplication and protecting the other macaque contacts against the infection, when 10 mg/kg were administered for 12 days.
The first case of infection in the United States of America received Remdesivir from the 7th day of hospitalization for pneumonia and the clinical status improved considerably, with no adverse reactions and a decline in viral load in the nasal swabs (12).
The mechanism of action consists of inhibiting the RNA polymerase of corona viruses by the active metabolite that acts as a nucleoside analog. The drug binds to the viral RNA-dependent RNA polymerase, where it enables the adding of three more nucleotides before the termination of the RNA transcription (13).
Although not associated with clinical improvement in patients receiving it (14), many studies show that it reduces the recovery time in patients with severe COVID-19 and the mortality (15), particularly in hospitalized patients with lower respiratory tract infections (16), with limited potential for drug-drug interactions (17). A study on hamsters infected with SARS-CoV-2 showed that the association between remdesivir and methylprednisolone not only led to a decrease in viral replication, but also reduced tissue inflammation (18).
The adverse effects include gastrointestinal symptoms, elevated transaminase levels and increase in prothrombin time, with the recommendation to monitor the renal function in those with low glomerular filtration rate (19).
By the end of 2020, WHO issues a conditional recommendation against administering remdesivir in hospitalized COVID-19 patients (20), but the drug is currently included in the treatment protocols.

Chloroquine and Hydroxychloroquine (Plaquenil)

Chloroquine is a drug used against malaria, discovered in 1934, while hydroxychloroquine is an analogue used particularly in autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis.
Their mechanism of antiviral action consists of increasing the endosomal pH, thus inhibiting the fusion between the SARS-CoV-2 virus and the cell membrane, inhibiting the glycosylation of the cellular ACE2 receptor (the angiotensin-converting enzyme) (21).
In vitro findings showed that 4-Aminoquinolines (the family including chloroquine and hydroxychloroquine) have variable effects compared to the *in-vivo* findings: chloroquine inhibits the *in-vitro* replication of the Ebola virus, but caused a worsening of the infection in Guinea pigs, without showing a difference in mortality in the case of lab mice and hamsters. In the case of the Epstein-Barr virus, it boosted the viral replication in cell cultures (22). Hydroxychloroquine demonstrated antiviral action against SARS-CoV-2 on a culture of renal cells of the green monkey, but no activity on a culture of human respiratory epithelial cells (23).
The most common adverse effect is a QTc prolongation, particularly in patients with an underlying heart condition

(especially in association with Azithromycin), hypoglycemia, neutron-psychiatric effects, genetic variability of metabolization influencing the safety and efficacy of the administration (24).
Intensively used in the first wave of the COVID-19 pandemic, the subsequent studies showed that the administration of hydroxychloroquine has no clinical or prophylactic benefits (25), despite its anti-inflammatory effect which decreases the production of cytokines and inflammatory factors in autoimmune diseases (26).
Azithromycin was recommended to patients infected with SARS-CoV-2 due to its antiviral effects - which are assumed to derive from the fact that it prevents the binding of the virus to the receptor, its effects on viral lysosomes, intracellular cell-signalling pathways and enhancement of type I and III interferon expression, coupled with immunomodulatory effects that may relieve inflammation and benefit tissue repair (27).
Used in other viral infections, where it proved helpful in reducing the production of inflammatory cytokines, preventing pulmonary fibrosis, as well as decreasing mortality and the number of days of mechanical ventilation, alongside *in-vitro* studies that showed the immunomodulatory effects through its capacity of interfering at various moments of the SARS-CoV-2 viral cycle (28), it initially proved to be a promising therapy.
Some of the adverse reactions include gastrointestinal events, QTc prolongation - the association with hydroxychloroquine being risky, with no clinical benefit or powerful antiviral effect (29).
The initial studies showed that in a 5-day treatment with a 500-mg dose on the first day and 250 mg in the following 4 days, a clinical improvement was seen in the first 24-48 hours, but since the patient sample was small (30), subsequent reviews indicated that the treatment with Azithromycin brings no benefits when used as therapy in patients confirmed or suspect of COVID-19, does not shorten the remission time, nor the hospitalization risk in comparison with the symptomatic medication (31). The RECOVERY Trial concluded that its use in COVID-19 patients has no benefits for the 28-day mortality, does not shorten the length of hospitalization and does not reduce the risk of mechanical ventilation (32).
Ivermectin is an antiparasitic drug, used to treat onchocerciasis, scabies or malaria. In the case of the SARS-CoV-2 infection, it has been demonstrated to inhibit the viral replication in cell cultures, but the dose needed for in-vitro administration is 100-fold higher than the dose approved for use in humans.
Some of the adverse reactions are dizziness, nausea, pruritus or diarrhea. The studies conducted for COVID-19 provide contradictory results (33).
Lopinavir/Ritonavir (Kaletra) is a drug used in the treatment of HIV infections, as a protease inhibitor. Proteases are enzymes contributing to the formation of viral structural proteins in the multiplication process. Kaletra is a combination of two substances, of which the main effect is due to lopinavir, as the ritonavir dose is inefficient, but increases the plasma lopinavir concentration (34).
Some of the adverse reactions include gastrointestinal symptoms (nausea, vomiting, diarrhea), QTc prolongation (high risk in association with hydroxychloroquine) and hepatotoxiticy. Through its cytochrome P450 3A inhibiting mechanism, it can increase the concentration of drugs that are coadministered, resulting in concentration-related toxicities (35).
With COVID-19, there was no clinical benefit from the administration of the treatment or a decrease of the viral load with lopinavir/ritonavir compared to the standard treatment (36), although a small study conducted on 47 patients showed a decrease of the time needed for the temperature to return to normal in those who ran a fever (37) and another one revealed that it can be associated with a decrease in mortality, risk of adverse reactions and developing acute respiratory failure with an acute respiratory distress syndrome (38).
The RECOVERY Trial showed that lopinavir/ritonavir is not associated with a decrease in the 28-day mortality, length of hospital stay, risk of invasive ventilation or death in COVID-19 patients, which supports the fact that it is not a treatment for hospitalized patients (39).
By the end of 2020, WHO adds to the treatment guidelines a strong recommendation against using lopinavir/ritonavir in COVID-19 patients, regardless of the severity of the disease (40).
Favipiravir is a an antiviral drug used to treat influenza in Japan. It is a pyrazine derivative that can be embedded in the viral RNA, where it mimics adenosine and guanosine, resulting in mutations in the production of RNA copies (41).
Starting from the studies conducted on hamsters infected with SARS-CoV-2, where favipiravir proved effective in decreasing the viral replication in lungs, inducing clinical improvement of the diseases and reducing lung tissue destruction (42), in the case of humans, favipiravir caused an increase of the viral clearance, improved chest CT scan on day 14 (43) and blood tests.
Some of the adverse reactions include an increase in liver enzymes, bilirubin and uric acid, gastrointestinal manifestations, but has a good safety profile (44).

Monoclonal antibodies

Bamlanivimab and Casirivimab are monoclonal antibodies neutralizing the binding receptor of the S protein in the SARS-CoV-2 virus genome. As the virus is easily susceptible to mutations, the treatment does not seem beneficial and its use is recommended only in clinical trials (45).

Convalescent plasma from patients that recovered from COVID-19 may contain antibodies that can suppress the virus and modify the inflammatory response. Some studies have demonstrated the benefit of using it in patients with primary or secondary immunodeficiencies, but other cases showed that the virus may become resistant. On February 4th, 2021, FDA limited its use to the patients hospitalized early or in those with humoral immunodeficiencies (46).

Specific and non-specific immunoglobulins

The use of SARS-CoV-2 specific or non-specific immunoglobulins is not recommended for the infection, due to the lack of data. They can be used only in clinical trials (47).

Corticosteroids

Corticotherapy has been used in SARS-CoV-2 infections due to the anti-inflammatory, antifibrotic and vasoconstrictive effects, but also because of the risk to develop ARDS in severe COVID-19 cases. The APROCCHSS, ADRENAL and DEXA-ARDS trials showed that patients with septic shocks or ARDS that required vasopressor therapy and received small doses of hydrocortisone hemisuccinate had a shorter period of mechanical ventilation, lower 90-day mortality and faster resolution of the septic shock (48).

Although widely used at first, it has been proven that using it in mild to moderate forms is not beneficial, but increases the length of hospital stay and the viral load (49). The current WHO recommendation concerns their use in severe or critical forms of the disease, in patients requiring oxygen (50), as they reduce mortality to approximately one third of the mechanically ventilated patients and to one fifth in those requiring oxygen, and can be used in pregnant women with severe forms, under the form of orally administered prednisone or intravenous hydrocortisone hemisuccinate (51). Combination therapy with tocilizumab in patients aged 65 or more with enhanced inflammatory syndrome proved beneficial for recovery (52).

The use of corticosteroids in severe forms of the disease has demonstrated a clinical benefit, without any differences when the dose administered was smaller or larger, as well as the fact that smaller doses do not impact the viral replication (53). The recommended dose is 6 mg of dexamethasone per day for 10 days, with the option to increase the administration time in select cases of severity with a risk of post-COVID lung fibrosis.

Some of the adverse effects include myopathies, neuromuscular weakness, psychiatric effects, high levels of coagulation factors and fibrinogen concentrations (54), with no risk of bacteremia or fungemia (55). At the same time, administering methylprednisolone (9 mg/kgc) in patients with hypoxemia appears to have had better results than administering dexamethasone, with a clinical improvement seen on days 5 and 10 (56).

In the latest recommendation, issued by the end of 2020, the OMS guidelines recommend using the corticotherapy in severe and critical forms of COVID-19, in patients requiring supplemental oxygen, a recommendation that does not apply to mild and moderate cases (57).

Inhaled corticosteroids were proposed as therapy due to the *in vitro* studies that showed inhibition of the viral replication of HCoV-229E coronavirus and a decrease in the cytokine production, while budesonide appears to block the replication of the SARS-CoV-2 viral RNA (58)., similar to cyclosenide in the study on cellular cultures, where the viral replication of MERS-CoV decreased (59).

The recommendation for treatment with inhaled corticosteroid in COVID-19 patients is to continue the existing therapy in patients known with asthma or COPD (60), in order to maintain the existing therapy, while benefiting from the effect of the drug on the prophylaxis of these patients, by decreasing ACE2 receptor, but starting to administer them without a certain diagnosis or increasing the dose in asthma patients is not recommended (58).

Interferons Alfa and Beta are part of a family of cytokines with antiviral effects. There is not sufficient data to show a benefit for COVID-19 (61).

Interleukin-1 Inhibitor (Anakinra) is an inhibitor of pro-inflammatory alpha and beta cytokines that was successfully used to treat the macrophage activation syndrome in inflammatory diseases (62).

In COVID-19 patients, its use is recommended in moderate-severe to critical forms of the disease where it was proved to reduce the risk of admission to an intensive care unit (63), mortality and need for mechanical ventilation (64). In these patients, the analysis of lung tissue fragments and bronchoalveolar fluids revealed a high level of profibrosis inflammatory monocytes, which seem to be the main inflammatory cells. Using Anakinra is safe, some of the adverse reactions being a slight increase of liver transaminases and triglycerides (65).

Interleukin-6 Inhibitor (Tocilizumab) is an inhibitor of interleukin-6, a proinflammatory cytokine produced by many body cells, including lymphocytes, monocytes and fibroblasts. The infection with SARS-CoV-2 induces a high production of bronchial epithelial cells, which is dose-dependent. At the same time, Il-6, together with the C-reactive protein, ferritin and D-dimers, play a key role in systemic inflammation and acute hypoxemic respiratory failure in COVID-19 (66).

The adverse effects include elevated liver enzyme levels, thrombocytopenia, neutropenia, skin rash and high risk for developing bacterial infections (67).

The use of Tocilizumab has proven to have a quick beneficial effect on fever and inflammatory markers, to reduce the need for oxygen and vasopressor support and the mortality[68], the risk to develop severe respiratory failure requiring mechanical ventilation (69,70) and may prevent irreversible lung injury (71).

Kinase Inhibitor - Baricitinib - inhibits the phosphorylation of key signaling proteins leading to immune activation and inflammation. JAK inhibitors (Janus Kinase), including baricitinib, have theoretical direct antiviral effects through interference with viral endocytosis, thus preventing the virus from entering and infecting the cell. Some of the adverse effects of its use include bacterial infections (respiratory and renal tract infections) and the reactivation of the herpes virus. There is no sufficient data for the use of Baricitinib in COVID-19, as it is approved for the treatment of rheumatoid arthritis (72).

Antithrombotic and anticoagulant therapy

The cytokine storm in COVID-19 leads to an endothelial dysfunction, with the risk of hypercoagulation translated into micro- and macro thrombosis, also supported by biological modifications: high levels of fibrinogen and D-dimer, increased prothrombin time and thromboplastine activation time, lower platelet count (73).

The thromboembolic events may consist of *in situ* microthrombosis of small vessels, a component of acute lung injury - which is also called immunothrombosis (74), up to thrombus formation in the main vessels. The American Society of Hematology reported a 69% risk of deep venous thrombosis (DVT) in critical patients (75) and recommends the administration of prophylaxis with anticoagulant in small doses for patients with acute or critical forms of COVID-19, irrespective of whether there is a DVT suspicion or not (76).

As regards the risk of bleeding, a study covering 615 hospitalized COVID-19 patients, of which 311 received therapeutic treatment with rivaroxaban or enoxaparin and 304 were given prophylactic therapy, shows that the therapeutic use of anticoagulants had no clinical benefit and increased the bleeding risk (77).

The anticoagulant treatment is recommended in patients that were already under an anticoagulant treatment recommended for other diseases or had clear signs of thrombosis, while patients confirmed or suspected of SARS-CoV-2 infection and treated at home may be given small doses of aspirin (78).

The WHO guidelines recommend the monitoring of patients for signs and symptoms of thromboembolism (infarction, deep venous thrombosis, pulmonary emboli or acute coronary syndrome) and, in case of suspicion, the proper diagnosis and treatment protocol must be initiated immediately (79).

Vitamins and food supplements have been intensively recommended to patients with mild or asymptomatic forms of SARS-CoV-2 infections treated in outpatient care, mostly due to the anti-inflammatory and anti-oxidant effects, but there is no sufficient evidence supporting the benefit they might bring (80).

Conclusion

The lack of specific treatment against the SARS-CoV-2 infection and the pressure on the healthcare system worldwide have led to extensive research aimed at finding therapeutic options. At present, a new antiviral drug (molnupiravir) opens the way to new promising alternatives for the infected patients, reducing the risk of progression to severe forms and acute respiratory distress syndrome (81).

At the time, the only efficient measure in combating the pandemic has been the prophylaxis through vaccination.

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