Covid-19 treatment options - from research to practice

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Introduction

As the disease continued to rise, more than 126 million SARS-CoV-2 infections were reported worldwide on March 26, 2021, and the virus has caused nearly 2.8 million known deaths. [1] The circumstances of the pandemic have required rapid and comprehensive research into treatment options for the virus and Covid-19. More than 3,700 clinical trials and an unprecedented number of scientific publications were officially registered during the pandemic. [2] However, despite the activity of the researchers and the resources invested, there are insufficient data on effective treatments. Research tends to be even contradictory. Another challenge is the critical approach to evaluating new data in an environment of rapidly changing circumstances and available information. Due to the lack of evidence, situations arise when off-label therapy is used in clinical practice or with a very low level of evidence, leading to questionable quality of treatment. With the growing understanding of the diverse mechanisms of Covid-19 pathogenesis, more therapeutic options are emerging, but the lack of effective etiological therapy remains one of the missing links in the Covid-19 high mortality and eradication chain.

In this article, we will look at the currently studied treatment methods and drugs, analyzing the data that confirm their effectiveness and safety in the treatment of Covid-19.

Treatment of SARS-CoV-2 infection

Oxygen therapy

Due to viral tropism and severe lung tissue damage, oxygen is currently the primary treatment for pneumonia due to SARS-CoV-2 infection. Supplemental oxygen therapy is indicated for

hypoxemic patients and virtually all currently available oxygen delivery methods are used depending on the degree of hypoxia. Oxygen target saturation levels vary from country to country, but it is assumed that supplemental oxygen supplementation is required for patients with SpO2 below 92-96%. This level of saturation is also defined as an achievable goal. A lower target is set for patients with chronic obstructive pulmonary disease, in this case 88-92%. It is also recommended to use the lowest possible oxygen supply and a less invasive method to ensure target saturation. [3]

Glucocorticosteroids

The use of glucocorticosteroids is recommended in patients with moderate, severe and critical disease (see Table 1) who require additional oxygen therapy. In the case of Covid-19, an active immune response is observed with gradual progression of the disease, which can be limited by glucocorticosteroid therapy. Current standard treatment includes dexamethasone 6 mg p / o or i / v, but equivalent doses of other glucocorticosteroids may be used. Dexamethasone is the main drug used in most studies. In RECOVERY, dexamethasone reduced ventilated patients by one-third (RR 0.65, p = 0.0003) and reduced mortality by 20% in oxygen-treated patients (RR 0.80; p = 0.0021), but did not affect mortality in the patient population. which did not require an additional oxygen supply. [4] This effect can be explained by the development of a systemic inflammatory picture that significantly affects the lungs, but additional oxygen therapy in this case serves as an indicator of the progression of the inflammatory process. Therefore, the immunomodulatory effect of dexamethasone is observed in patients with moderate, severe and critical disease.

Anticoagulants

In the case of SARS-CoV-2 infection, a state of hypercoagulability is observed, the pathogenesis of which is not entirely clear - mostly microthromboses in various organ systems. Thrombosis is particularly common in patients with severe disease. All elements of the Virhov triad are of great importance. Endothelial damage is considered to be the most important factor, as viral invasion of vascular cells is observed, as well as a systemic inflammatory response, thus contributing to endothelial damage. Vascular stasis and changes in the coagulation cascade are also observed. [5] Therefore, all hospitalized patients receive anticoagulant therapy, most commonly low molecular weight heparins such as enoxaparin subcutaneously, in the absence of contraindications. Prophylactic doses of anticoagulants are generally used, but therapeutic doses are used as the disease progresses and / or other prothrombotic risk factors exist.

In a large cohort study of 4297 patients, prophylactic anticoagulant use reduced the overall risk of death in hospitalized patients by 27%. [6]

However, this type of treatment increases the risk of bleeding, and the use of anticoagulants may not always prevent Covid-19 patients from developing thrombosis. The risk of thrombosis is thought to decrease as the systemic inflammatory response decreases. There is less consensus

on the need to use anticoagulants after discharge from hospital, so it is assessed on an individual basis.

Remdesivir

The viral RNA polymerase inhibitor remdesivir is an antiviral medicine that inhibits viral RNA synthesis, thereby inhibiting viral replication. It is designed to treat hepatitis C and has also been tried during the Ebola epidemic. Remdesivir showed good efficacy in initial in vitro studies, but this efficacy has not been confirmed in clinical trials. One explanation is that in in vitro studies, the drug was used at a very early stage of the experimental infection, but it cannot be used in SARS-CoV-2 infection because no symptoms are observed in the patient during this period. Nevertheless, in the ACTT-1 study, the median recovery time was 10 days in the study patients treated with remdesivir and the median recovery time was 15 days in the placebo patients. [7]

Unfortunately, the same study data suggest that the drug has no significant effect on disease outcome such as mortality or progression of patients with the need for artificial lung ventilation. Due to the lack of evidence of significant efficacy of remdesivir, its high cost and its potential for hospital use only (the drug is only available in IV form), the World Health Organization does not currently recommend its use. [8] The data in the guidelines differ, so in Latvia the use of remdesivir is decided by the medical council and is mainly used in hypoxemic patients up to the 10th day of illness. It is expected that the indications for remdesivir will be re-examined in the future once additional efficacy data are available.

Other medicines studied in the treatment of Covid-19

In addition to the above-mentioned medicines, studies of various qualities have also been performed with other medicines, which due to insufficient evidence in most countries, including Latvia, are currently not included in the national recommendations. Relatively high-quality studies published in English have looked at antivirals such as the lopinavir / ritonavir combination and favipiravir, as well as immunomodulatory agents such as hydroxychloroquine, colchicine, tocilizumab, anakinra, baricitinib, some intravenous immunoglobulins, convalescent Contradictory data on the effects of these and other drugs have also been published in many lower-quality, small-scale studies.

All of these drugs have been previously developed and used to treat other viral and autoimmune diseases, and their theoretical application in the treatment of SARS-CoV-2 infection is based on inhibition of two disease pathogenesis processes: viral replication and cytokine storms or massive exaggerated immune responses. In the study of pathophysiological processes during SARS-CoV-2 infection, in vitro effects have been observed with some of the drugs used in the studies, but not always to a significant clinical benefit. It should be noted that the number of patients enrolled in clinical trials varies widely, often by less than a hundred, as well as the inclusion and exclusion criteria, the severity of the patient's disease, the standard therapy used, and the outcome - death, severe, mechanical ventilation, hospitalization. time, clinical improvement, etc., which makes it difficult to compare studies and produce different results.

Antibacterial therapy

Basic therapy does not include the use of antibacterial agents, as they are intended to treat bacterial infections, but given that SARS-CoV-2 is a virus, its replication and viability are not affected by these agents. Only 2-7% of SARS-CoV-2 infections are associated with secondary bacterial infections treated with antibacterial therapy. [9]

Antivirals

In this group of medicines, convincing data on recovery benefits and mortality reduction have only been obtained for remdesivir. The following is a brief description of the available evidence on the efficacy or lack of the studied drugs.

Lopinavir / ritonavir

Lopinavir is a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor, while ritonavir prolongs its half-life. Antiviral activity was observed with this combination in vitro, but two clinical trials in Covid-19 did not show significant improvement over standard therapy in terms of duration of fever, time to hospitalization, time to clinical improvement, reduction of mortality and viral load. [10,11]

Favipiravir

The RNA polymerase inhibitor favipiravir, which has an in vitro antiviral activity against SARS-CoV-2 in a recently published small randomized study, did not show statistically significant benefits in terms of mortality, but patients treated with the drug tended to have a shorter hospital stay. [12]

Immunomodulatory agents

Hydroxychloroquine

Hydroxychloroquine is a classic drug used to treat malaria and a number of rheumatological diseases. It prevents an excessive immune response and inhibits the binding of SARS-CoV-2 to ACE-2 receptors in vitro.

In the spring of 2020, reports were published from China on a series of cases in which clinical improvement was observed with hydroxychloroquine in Covid-19 patients. This was soon followed by a small non-randomized study from France with promising results in terms of viral load reduction, where hydroxychloroquine was combined with azithromycin. [13] The study was criticized for its methodological shortcomings. In retrospective studies, hydroxychloroquine did not reduce or even increase mortality in Covid-19 patients. [14,15] In a study of 665 patients, hydroxychloroquine did not improve the clinical course of the disease with or without azithromycin. [16] A significant side effect of hydroxychloroquine was QT prolongation with an increased risk of arrhythmias. Several other randomized studies also failed to show a plausible difference in mortality between the hydroxychloroquine and placebo groups. In one study in the hydroxychloroquine group, disease progression was more common - artificial lung ventilation was required. [17,18]

Tocilizumab

Tocilizumab is a monoclonal antibody to the interleukin-6 (IL-6) receptor. This class of drugs was of particular interest in the treatment of Covid-19 patients, given the important role of IL-6 in the pathogenesis of the disease and in the course of cytokine storms. In five randomized studies in patients with at least moderate disease, no significant differences in mortality were observed between the drug and placebo groups. [19,20,21,22,23] In the CORIMUNO-19 study, there was a lower progression to a combined outcome of non-invasive ventilation, invasive mechanical ventilation therapy, or death, but 28-day mortality did not differ between study groups. Similar results were seen in the EMPACTA study in hypoxic patients with SARS-CoV-2 pneumonia, where tocilizumab treatment reduced the combined outcome of invasive mechanical ventilation or death, but did not increase patient survival in this study. In contrast, in the REMAP-CAP study, which included Covid-19 critically ill patients, patients receiving tocilizumab had lower in-hospital mortality (28.0% vs. 35.8%) and higher 90-day survival. An improvement in 28-day mortality in hypoxic patients was also observed in the RECOVERY study, 29% in the tocilizumab and 33% in the control group. In contrast, in the study, patients requiring oxygen therapy had an even higher 15-day mortality in the tocilizumab group than in the standard care group, so the study was terminated prematurely. Consequently, the results of the performed research can be assessed as ambiguous.

The REMAP-CAP study also looked at another IL-6 inhibitor in a small group of patients, sarilumab, which reduced nosocomial mortality and increased the number of days without organ support in critically ill patients. In contrast, a randomized study of 416 oxygen-dependent patients published in March 2021 showed no improvement in recovery or mortality after receiving sarilumab. [24]

Convalescent plasma

One of the methods of treating Covid-19 at the beginning of the pandemic was to use plasma from diseased patients to deliver antibodies to SARS-CoV-2 in the blood of a sick patient. In the three randomized studies, no significant differences were observed between study groups in terms of mortality, disease progression, or clinical improvement over 28 or 30 days. [25,26,27]

Baricitinibs

The ACTT-2 study evaluated the efficacy of the rheumatoid arthritis drug baricitinib in the JAK inhibitor group. In this study, hospitalized Covid-19 patients receiving remdesivir in combination with baricitinib had a median time to recovery of 7 days, compared with 8 days in patients receiving remdesivir and placebo. This difference was statistically significant but clinically insignificant. In contrast, patients who were already receiving high-flow oxygen therapy or non-invasive ventilation at the time of enrollment had a recovery time of 10 days, compared with 18 days, respectively. No differences in mortality were observed. [28]

Colchicine

The anti-inflammatory drug colchicine Covid-19 used to treat exacerbations of gout and pericarditis has been studied in two randomized clinical trials. The theoretical basis for the action of colchicine is the inhibition of NLRP3 inflammatory activation of cells, which is important in the induction of cytokine storms. In a study of 105 patients in the colchicine group, clinical deterioration was uncommon. [29] A large Canadian study in patients at risk with

Covid-19, involving a total of 4,488 initial outpatients, compared colchicine (0.5 mg twice daily for three days, then once daily) with placebo for 30 days. . The combined primary endpoint in this study was death and hospitalization for Covid-19. There was no statistical significance in contrast to the colchicine and placebo groups, but a statistically significant (albeit small) differences in outcome rates of 4.6% in the colchicine group and 6.0% in the placebo group, respectively, p = 0.04. [30] It should be noted that this study was terminated prematurely and the primary outcome did not in fact reach statistical reliability, therefore the results should be treated with caution.

Other immunomodulatory agents

A US-developed cocktail of two artificial monoclonal antibodies, REGN-COV2, containing cassirivimab and imdevimab, has been approved in Europe for use in patients who do not require oxygen therapy but are at high risk for severe Covid-19. Another promising monoclonal antibody is bamlanivimab. These antibodies bind to different regions of the SARS-CoV-2 peak (spike) protein. However, these drugs are not currently recommended for routine use in Covid-19 patients due to a lack of results from phase III studies on their efficacy.

Other immunomodulatory agents such as anakinra, ruxolithinib, interferon beta, intravenous immunoglobulins (IVIG), vilobelimab have also been evaluated in randomized studies. Interferon beta studies have published controversial results. Only the first of these studies showed lower mortality in treated patients, but no evidence of reduced need for oxygen support and non-invasive or invasive mechanical ventilation. [31] Intravenous immunoglobulin therapy has been studied in two randomized trials. In a study of 59 patients with severe Covid-19 in the IVIG group, hospital mortality was significantly lower at 20% versus 48%. [32] In another study of 84 patients with severe Covid-19, no benefit was observed in terms of mortality and the need for mechanical ventilation. [33]

Other monoclonal antibodies or kinase inhibitors have been considered in small prospective non-randomized studies, but no conc**lusive evidence of a positive effect has been obtained.**

Ivermectin

The antiparasitic drug ivermectin has generated interest in the therapeutic potential of Covid-19 because it inhibits alpha / beta-1 nuclear transport proteins used by viruses to reduce the immune response in vitro. Ivermectin may also interfere with the binding of the SARS-CoV-2 spike protein to the cell membrane. However, no significant improvement in the clinical course of Covid-19 was observed in any ivermectin study. [34]

Conclusions

Glucocorticosteroids, oxygen and anticoagulants are currently well established and clinically relevant in the treatment of Covid-19 infection. The efficacy of other investigational drugs is unclear or controversial, and is not based on conclusive evidence, in some cases leading to adverse effects on disease outcome. As the Covid-19 pandemic continues, it is essential to develop common international guidelines and coordinated cooperation between research centers. It is particularly important to reduce the use of insufficiently proven treatments in clinical practice, as well as to ensure the timely inclusion of new and promising treatment options in patient care.

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