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COVID-19 and Cardiovascular System. Part 3. COVID-19 Current Treatment Approaches: Evidence-Based Review

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ABSTRACT Unified management plan and treatment strategy for COVID-19 patients are yet to be discovered. Many trials on COVID-19 interventions have been registered or are ongoing. In this article the results of large-scale clinical trials on COVID-19 treatment are presented, the potential mechanism of action of some drugs is discussed, the features of the main pharmacological and non-pharmacological therapeutic options for COVID-19 patients are described.

Keywords: COVID-19 treatment, clinical trials, therapeutic options for COVID-19, anti-SARS-CoV-2 antibody products, antiviral therapy, immunomodulators, antithrombotic therapy, non-pharmacological interventions

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AH — arterial hypertension
BMI — body mass index
CKD — chronic kidney disease
COPD — chronic obstructive pulmonary disease)
CP — convalescent plasma
CRP — C-reactive protein
CVD — cardiovascular disease
DM — diabetes mellitus
ECMO — extracorporeal membrane oxygenation
GCSs — glucocorticosteroids
IL — interleukin
JAK inhibitors — Janus kinase inhibitors

MABs — monoclonal antibodies
MLV — mechanical lung ventilation
NABs — neutralizing antibodies
PCR — polymerase chain reaction
PCs — plasma cells
RCCT — randomized controlled clinical trial
RF — risk factor
Sp-p — spike protein
t-He/O_2 — helium-oxygen mixture

INTRODUCTION

The development of effective and safe methods of treatment and prevention of COVID-19 is an urgent task for the medical community at present. Management of patients with coronavirus infection is a complex and unpredictable process that must take into account both the current state of the patient and his concomitant diseases and be based on carefully developed recommendations with a high degree of reliability. The rapid development of the evidence base requires a reliable interpretation and systematization of data to be included in clinical practice in the form of guidelines to inform clinicians and healthcare professionals as soon as possible.

Medical professionals, patients, and healthcare decision makers, as well as government agencies, have encountered problems with interpreting the results of clinical trials, which are being published at a rate that has never been seen before. This creates a problem of distinguishing reliable evidence from unreliable ones, which results in the choice of treatment tactics with a low level of evidence.

To develop the most effective proven treatment regimens, timely systematic synthesis of published data is required. It is necessary to implement the latest solutions in the field of drug therapy into clinical practice, if they have a sufficient degree of evidence. At the moment, there is no unified strategy for managing and treating patients for COVID-19, but over time and during the completion of clinical trials, the information base is being updated, which makes it possible to introduce more effective treatment methods into clinical practice.

I. KEY CLINICAL TRIALS OF COVID-19 THERAPY

At the moment, more than 2,800 studies investigating drug and non-drug therapy for COVID-19 have been registered worldwide [1]. These are national and international studies with a pragmatic and adaptive design that involve a large number of patients. These studies evaluate the efficacy of multiple approaches to the treatment of COVID-19 and associated conditions, both in terms of individual drugs and drug combinations. The largest of all current clinical trials are RECOVERY (Randomized Evaluation of Covid-19 Therapy) and SOLIDARITY.

RECOVERY TRIAL

The RECOVERY trial is the largest open-label multicenter randomized controlled clinical trial (RCCT) conducted in 176 public hospitals in the United Kingdom, and was launched in March 2020 by a team of scientists from the University of Oxford. The aim of the study is to evaluate the efficacy and safety of several drugs with potential effect in the treatment of hospitalized patients with COVID-19: azithromycin, colchicine, plasma of convalescents, dexamethasone, hydroxychloroquine, lopinavir and ritonavir, and tocilizumab [2-3]. The study is of adaptive design, meaning that some non-promising drugs can be excluded from it and new drugs can be added.

According to the results of the study, only two drugs listed above, dexamethasone and tocilizumab, are effective in terms of beneficial effects on the endpoints in hospitalized patients [4-11]. Currently, the evaluation of drugs includes: REGN-COV2 (a "cocktail" of two specific monoclonal antibodies), baricitinib, dimethyl fumarate, infliximab, higher dosages of dexamethasone and aspirin. Low-dose dexamethasone, intravenous immunoglobulin, tocilizumab, and anakinra were included in the evaluation of medicines for the treatment of children with paediatric inflammatory multisystem syndrome (PIMS-TS).

SOLIDARITY TRIAL

SOLIDARITY is an international clinical trial initiated by WHO and its partners to find effective medicines for the treatment of COVID-19. This is one of the largest international RCCTs of drugs against COVID-19 implemented with the participation of almost 12,000 patients in 500 hospitals in more than 30 countries. As part of the study, the efficacy of drugs is evaluated according to three criteria for the outcome of the disease in patients with COVID-19: the length of hospital stay, the need for mechanical lung ventilation (MLV), and death.

Initially, the study objects were hydroxychloroquine, remdesivir, lopinavir/ritonavir, and interferon beta-1a. The study found that these drugs have no or almost no effect on all 3 criteria for the outcome of the disease in hospitalized patients. However, these results relate only to the SOLIDARITY Trial in hospital patients and do not affect the possible evaluation conducted in other studies of hydroxychloroquine and lopinavir/ritonavir among non-hospitalized patients or as a pre- or post-exposure prevention of COVID-19. In addition, the study is of adaptive design, and also includes trials that are within the SOLIDARITY framework, for example, on the use of vaccines [12].

II. THE MAIN TRENDS IN THE SEARCH FOR TREATMENT METHODS FOR COVID-19

Despite the global scale of efforts to identify effective treatments and prevent COVID-19, data for unambiguous approval of the efficacy of a particular therapy is still limited. The British Medical Journal (BMJ), together with WHO, launched the BMJ Rapid Recommendations project. It provides a meta-analysis-based evidence base on drug therapy that underpins WHO's real-time updated recommendations for the treatment of COVID-19. Currently, the fourth version of the meta-analysis has been published, which includes published and unpublished data from global randomized controlled clinical trials (RCCTs), with the exception of trials on the use of drugs based on specific antibodies. Highlights of the latest meta-analysis: corticosteroids and interleukin-6 (IL) inhibitors probably have advantages in terms of fatal outcome in patients with severe COVID-19; in patients without severe course of the disease, mortality may be decreasing with colchicine; therapy with Janus kinase (JAK) inhibitors and remdesivir can reduce the need for mechanical lung ventilation, but the data are limited, the need for mechanical ventilation appears to be falling with glucocorticosteroids (GCS) therapy and IL-6 inhibitors; azithromycin, hydroxychloroquine, lopinavir-ritonavir and beta-interferon, apparently do not have any important advantages with respect to clinically relevant outcomes; evidence for the benefits of the use of ivermectin and other drugs is limited [13].

The fourth version of the guidelines includes the guidance on ivermectin in response to international attention for the drug as a potential treatment for COVID-19. The first version was published on September 2, 2020, and contained recommendations for glucocorticosteroids (GCS) [14]; the second version (in November 20, 2020) contained those for remdesivir [15]; the third one (in December 12, 2020) had recommendations for hydroxychloroquine and lopinavir/ritonavir [16]. In the fourth version of the guidelines, there are no changes for any of these drugs. A detailed description of some medications is provided below.

II.1 ANTI-SARS-COV-2 ANTIBODY THERAPY

MONOCLONAL ANTIBODIES

Monoclonal antibodies (MAs) are lab-developed molecules designed to mimic or enhance the body's natural immune system response against a foreign agent, an antigen. Potentially, MAs have advantages over other types of treatment, since they are designed specifically to target a certain key part of the infectious process development. A monoclonal antibody is created by exposing immune cells to a specific viral protein, which is then cloned to mass-produce antibodies targeting that virus. Prior to COVID-19, there were MAs developed to treat several viral infections, such as Ebola and rabies. On its surface, SARS-CoV-2 has a spike protein (S-protein) that helps the virus attach and enter cells. Several MAs have been developed that bind to the spike protein (Sp-p) of SARS-CoV-2 and block the virus from entering human cells [17].

Bamlanivimab/etesevimab

Bamlanivimab (formerly known as LY-CoV555) and etesevimab (formerly known as LY-CoV016) are experimental intravenous neutralizing MAs of human immunoglobulin G-1 with the activity against SARS-CoV-2. The two antibodies bind to different but overlapping epitopes of the Sp-p receptor-binding domain and block the virus from entering the body's cells. In the United States, emergency use authorization of bamlanivimab/etesevimab for the treatment of mild to moderate disease in children and adults has been approved [18-19].

Due to the growing prevalence of bamlanivimab-resistant SARS-CoV-2 variants in the United States, the authorization for emergency use of bamlanivimab monotherapy was revoked [20]. In phase 2-3 of the BLAZE-1 RCCT, which included 577 outpatients with mild to moderate COVID-19, various doses of bamlanivimab monotherapy (700, 2500, and 7000 mg) and bamlanivimab/etesevimab combination therapy (2,800 mg of each drug) were compared with placebo. During the first month of the study, despite the general trend towards a decrease in the number of emergency medical visits or a decrease in the probability of hospitalization in both groups compared to placebo (1-2% vs. 5.8%), a statistically significant difference was observed only in the combination therapy group [21].

In BLAZE-1 phase 3, 1,035 patients with mild to moderate COVID-19 who had risk factors (RFs) for severe diseases were randomly assigned to receive a single infusion of bamlanivimab/etesevimab (2,800 mg of each drug) or placebo.

According to preliminary results of the study, after one-month follow-up, the hospitalization or mortality rates were lower among those who received the combined bamlanivimab/etesevimab compared to placebo. All 10 deaths among the study participants occurred in the placebo group. Nausea and side effects (fever, rash) associated with the infusion were reported, but these side effects were generally rare and easily tolerated. However, the whole trial results are not available for analysis. The results of the phase 3 trial reflect a dose of 2800 mg of each drug, although the emergency dose for combination therapy is 700 mg of bamlanivimab and 1400 mg of etesevimab. The reduced dose is based on virological and clinical data, as well as pharmacokinetic modeling, which suggests that the lower dose is expected to have equal clinical efficacy to the combined dose of 2800 mg. However, the actual efficacy of the reduced dose is unknown [19].

CAZIRIVIMAB/IMDEVIMAB

Cazirivimab and imdevimab are experimental intravenous neutralizing MAs of human immunoglobulin G-1 with the activity against SARS-CoV-2. Two antibodies bind to non-overlapping epitopes of the Sp-p receptor-binding domain and block the virus from entering the body's cells. In the United States, an emergency use authorization of casirivimab/imdevimab (formerly known as REGN-COV2) has been approved for the treatment of mild to moderate disease in children and adults [19].

In an RCCT that included 4,180 outpatient patients with mild to moderate COVID-19 who presented with RFs of severe course of the disease, the combination of casirivimab and imdevimab at two different doses (total 1200 and 2400 mg) was compared with placebo [22, 23]. An unpublished preliminary report for 29 days of follow-up showed a decrease in the cumulative outcome of hospitalizations and mortality compared to placebo in both the group of those who received 1200 mg of each drug, and in the group of those who received 2400 mg (1200 mg of the total dose: 1% vs. 3.2%; 2400 mg of the dose: 1.3% vs. 4.6%). In earlier trials, the use of a combination of these drugs was associated with rare side effects, including fever, chills, hives, abdominal pain and redness at the injection site, which were related to the intravenous infusion of the drug. One episode of anaphylaxis was also reported [24, 25].

The use of MAs is intended for outpatients with a mild or moderate course of COVID-19, who have a certain risk factor for severe disease. These RFs for persons 18 years of age and older include any of the following:

— body mass index (BMI) ⩾35 kg /m2;
— chronic kidney disease (CKD);
— diabetes mellitus (DM);
— immunosuppression (therapy or treatment);

— age 65 years and older.

— age 55 years and older in combination with the presence of cardiovascular diseases (CVDs), and/or arterial hypertension (AH), and/or chronic obstructive pulmonary disease (COPD), or other chronic respiratory diseases.

MAs should be administered as a single intravenous dose as soon as possible after a positive test result for SARS-CoV-2, but no later than 10 days after the onset of symptoms. There are limited data based on indirect evidence of the effect of antibody therapy on the viral load and natural course of COVID-19, confirming their increased efficacy with earlier administration. To achieve maximum efficacy, it is preferable that MA therapy, if used, is carried out within 3 days after the onset of symptoms [26].

In the United States, patients with COVID-19 can receive an intravenous MA infusion, usually at an emergency department or infusion center. Hospitalized patients can receive MA only in clinical trials or under special circumstances, if they meet the criteria for MA administration [27]. The results of available studies do not yet demonstrate the proven efficacy of using MAs in hospitalized patients [28].

REGDANVIMAB

Regdanvimab (formerly known as CT-P59) is an investigational neutralizing MA with the activity against SARS-CoV-2. Regdanvimab has been granted conditional authorization certificate in South Korea for the treatment of adults with mild symptoms aged 60 years and older or at least with one underlying medical condition, as well as all adults with moderate symptoms. The European Medicines Agency recommends the use of regdanvimab in the treatment of adult patients with confirmed COVID-19 infection who do not require oxygen therapy and who are at a high risk of progressing to severe disease [29].

According to the manufacturer's press release, regdanvimab reduces the incidence of mild-to-moderate to severe disease progression by 50%, and moderate to severe by 68%. However, the results of phase 2/3 studies have not yet been published [30]. Regdanvimab has also been shown to neutralize major new mutations, including variant B.1.1.7 [31].

CONVALESCENT PLASMA

Convalescent plasma (CP) is a blood product obtained from donors who have been ill with and cured from COVID-19. The main active component of such plasma is already existing anti-SARS-CoV-2 antibodies, which provide passive immunity. It is believed that other immune mediators contained in such plasma may also contribute [32].

According to preliminary data from the British RECOVERY Trial, CP with a high antibody titer does not improve survival or other pre-defined clinical outcomes in hospitalized patients [33]. It is assumed that CP containing high titers of neutralizing antibodies (NAs) has clinical benefits when administered at an early stage of the disease and may be of particular interest for people with a deficiency in antibody production (for example, those receiving anti-CD20 therapy), but data are limited [32].

In RCCI with the participation of 160 elderly people, with one or more concomitant diseases (hypertension, COPD, diabetes on pharmacotherapy, CVDs, CKD on hemodialysis, obesity), with a positive result of polymerase chain reaction (PCR) assay for SARS-CoV-2 and mild COVID-19 course, an early administration of CP was compared to placebo. High-titer CP therapy administered within 72 hours of the onset of symptoms reduced the risk of developing severe respiratory disease compared to placebo (16% vs. 31%) [34].

Trials evaluating CP administered later during the disease to outpatients with mild course have not shown equal efficacy. For example, a clinical trial of CP administered to persons 18 years and older with a mild form of the disease and one or more RFs of severe disease within 7 days after the onset of symptoms was discontinued due to the lack of a clinical effect [35].

Given the short window of opportunity for administration (within 72 hours of the onset of symptoms) and the additional technical challenges of intravenous administration in an outpatient setting, this therapy can only have a practical role in the management of eligible elderly people with mild COVID-19 in a skilled nursing setting. As in case of MA therapy, the therapy with a high titer CP remains experimental.

SPECIFIC IMMUNOGLOBULIN PREPARATIONS

The use of specific immunoglobulins has found its application in the treatment of some viral infections. For example, citomegalovirus immunoglobulin preparations have proven to be safe and effective in preventing post-transplant infection, as well as virus-specific Varicella zoster immunoglobulin in post-exposure prophylaxis in people at a high risk of infection [36].

Intravenous immunoglobulin for COVID-19 is a product from the plasma of healthy donors who have had a coronavirus infection, which contains a high concentration of antibodies. The expected effects of such therapy are: an immunomodulatory effect and imitation of the natural immune response, a reduction in the disease course duration and rehabilitation time [37].

Currently, there are no convincing data on the efficacy and safety of this type of treatment at any stage of the disease course. A recently completed RCCT, which involved 285 patients admitted to a Chinese clinic, showed the ineffectiveness of such therapy in severe cases of COVID-19 and the lack of the effect on the specified endpoints [38]. Data on the effects of intravenous immunoglobulin in the treatment of children with severe disease and in outpatient practice are limited. Currently, the use of intravenous immunoglobulin is recommended only in clinical trials [36, 39].

II.2 ANTIVIRAL THERAPY

REMDESIVIR

Remdesivir is a direct-acting antiviral agent that is a nucleoside prodrug. In the body, the active metabolite of remdesivir, as an analog of adenosine nucleoside triphosphate, interferes with the action of viral RNA-dependent RNA polymerase, an enzyme necessary for viral replication.

The drug has been shown to be effective against SARS-CoV-2 in vitro, and subsequently in laboratory animal models [40]. Remdesivir has been studied as a treatment for COVID-19 in several clinical trials, with conflicting results [41]. The ACTT-1 (Adaptive COVID-19 Treatment Trial), which included 1,062 patients, identified some benefit of remdesivir for patients who needed additional oxygen support [42]. Among the results of this study, there was also a slight decrease in the time to recovery. Remdesivir is currently approved for the treatment of COVID-19 in hospitalized adults and children (aged 12 years and older, weighing 40 kg or more). Also, through a special approval from the Food and Drug Administration (FDA), the drug is available for emergency use in the treatment of COVID-19 in hospitalized children weighing 3.5 to 40 kg or under the age of 12 years with a weight of 3.5 kg or more. However, remdesivir should only be prescribed in a hospital or medical facility that can provide a similar level of hospital care.

IVERMECTIN

Another promising object for clinical trials is a drug that is mainly used in veterinary practice for the treatment of endo- and ectoparasitic diseases of animals [43]. In humans, ivermectin is an antiparasitic drug that is used to treat certain tropical diseases, including onchocerciasis, helminthiasis, and scabies [44].

The proposed mechanism of action is based on the inhibition of a number of host transport proteins that the virus uses to enter the cell by inhibiting the antiviral response. In addition, the antiviral effect of the drug is probably based on the fact that, when embedded, ivermectin prevents the SARS-CoV-2 S-protein from attaching to the cell membrane. All these data were obtained in in vitro studies [45, 46]. The journal Antiviral Research published the results of the research of the Australian virologists, who by using the culture of infected with the virus SARS-COV-2 cells demonstrated in vitro that a single add of ivermectin to the culture was enough to reduce the number of viral particles in a day by 93% in the supernatant, according to PCR, and by 99.8% in the cells, thus achieving non-toxic concentrations. After 48 and 72 hours, no viruses were detected in the cell culture; no toxic effect or cell damage was recorded [47].

II. 3 REGULATION OF THE IMMUNE RESPONSE

Based on follow-up of patients with COVID-19, it was hypothesized that in mild cases, resident macrophages that initiate inflammatory responses in the lungs were able to restrain the viral invasion after SARS-CoV-2 infection; both innate and adaptive immune responses were effectively established to restrain viral replication. However, in severe or critical cases of COVID-19, the integrity of the air–blood barrier is

compromised. In addition to epithelial cells, SARS-CoV-2 can attack endothelial cells of the pulmonary capillaries, which leads to the appearance of a large amount of exudative component in the alveolar space. In response to SARS-CoV-2 infection, alveolar macrophages or epithelial cells can produce various pro-inflammatory cytokines and chemokines. As a result of these events, monocytes and neutrophils move chemotaxically from the site of infection to the general bloodstream, which leads to uncontrolled inflammation.

It should be noted that due to a significant decrease in the lymphocyte population and dysfunction, the initiated immune response becomes maladaptive. Uncontrolled viral infection leads to an intensification of macrophage penetration and further aggravation of lung damage. Meanwhile, a direct viral attack on other organs by spreading SARS-CoV-2, as well as a "cytokine storm" with an associated microcirculatory dysfunction, lead to a phenomenon that, in general, can be called viral sepsis. Therefore, effective measures to modulate the innate immune response and restore the adaptive immune response are of great importance for breaking the vicious circle and improving patient outcomes [50].

COLCHICINE

Several potential mechanisms of inhibition of proinflammatory reactions were used to initiate research on colchicine in the treatment of COVID-19. These mechanisms include decreased neutrophil chemotaxis, suppression of inflammatory signals, and decreased production of cytokines such as IL-1 beta. Along with this, the drug does not have a pronounced immune-suppressive effect, it is available, and it is also sufficiently studied for side effects [51].

The main studies investigating colchicine in the treatment of COVID-19 are the RECOVERY, GRECCO-19, and COLCORONA trials. Preliminary results of the RECOVERY and GRECCO-19 trials indicate a low proven efficacy of colchicine in hospitalized patients, and therefore, the drug is not recommended for use in a hospital setting outside the context of clinical trials [52, 53]. However, more interesting is the study of the drug in outpatient settings. The results of the COLCORONA Trial were published in The Lancet. This study included 4,488 patients over 40 years of age, 4,159 of whom were confirmed by PCR to have COVID-19; the rest were clinically confirmed. Patients of the main group were prescribed colchicine 0.5 mg twice a day for 3 days, then 0.5 mg once a day, patients of the comparison group received placebo. The follow-up period was 30 days.

Colchicine has been shown to reduce the risk of mortality and hospitalization in outpatients with PCR-confirmed COVID-19 compared to placebo. Given the lack of oral medications to prevent complications of COVID-19 and the demonstrated benefit of colchicine in patients with PCR-confirmed COVID-19, this anti-inflammatory agent may be considered for use in individuals with one or more risk factors for developing a complicated form of COVID-19 [54].

FLUVOXAMINE

Currently, scientists are considering similarities of severe COVID-19 course and sepsis [55]. One drug that has previously been shown to reduce tissue damage caused by inflammation, as well as reduce the effects of shock in sepsis in laboratory mice, is fluvoxamine. Fluvoxamine is a drug from the group of selective serotonin reuptake inhibitors, which is used to treat obsessive-compulsive disorder and depression. In addition, the drug has some anti-inflammatory effect due to its high affinity for S1R receptor inside cells. This protein is localized in the endoplasmic reticulum and performs many functions, including the regulation of cytokine synthesis through interaction with the inositol-dependent enzyme 1a (IRE1) [56]. In addition, in the studies of human endothelial cells and macrophages in vitro, fluvoxamine reduces the expression of genes responsible for the inflammatory response [57].

A small RCCT was conducted to evaluate the efficacy of fluvoxamine in preventing the progression of mild COVID-19. Preliminary results showed that adult outpatients had a lower probability of clinical deterioration within 15 days compared to placebo, but the study was limited by a small sample size and a short follow-up period [58]. Currently, there is no reliable evidence either for using this drug in the treatment of patients or against it.

INTERLEUKIN INHIBITORS

IL-6 is a pleiotropic, pro-inflammatory cytokine produced by various cell types, including lymphocytes, monocytes, and fibroblasts. SARS-CoV-2 infection associated with severe acute respiratory syndrome (SARS) causes dose-dependent production of IL-6 by bronchial epithelial cells. Systemic inflammation associated with COVID-19 and hypoxic respiratory failure may be associated with increased cytokine release, as indicated by elevated levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin.

The reduction of IL-6 levels and/or its pro-inflammatory properties is suggested to reduce the duration and/or severity of COVID-19 disease [59-62]. There are two classes of approved IL-6 inhibitors: MAs against IL-6 receptors (e.g. sarilumab, tocilizumab) and MA against IL-6 (siltuximab). These drugs were evaluated for the treatment of patients with COVID-19 who developed a systemic anti-inflammatory response. The data obtained from many clinical trials are contradictory, but there are encouraging results regarding tocilizumab and its positive effect on the transfer of patients to mechanical ventilation and a 28-day mortality, especially when co-administered with dexamethasone. In this regard, the drug is recommended for use in cases of severe COVID-19 with concomitant pneumonia and is contraindicated in people with immunodeficiency [63-65]. Sarilumab has a similar mechanism of action to tocilizumab, but there are currently no reliable data for either these drugs or siltuximab, and their use can only be justified in clinical trials [64, 66].

IL-1 is a pro-inflammatory cytokine that is produced by activated macrophages, keratinocytes, stimulated B cells, and fibroblasts. Elevated IL-1 levels are reported in patients with severe COVID-19. An increase in IL-1 is associated with a cytokine storm during therapy with T-lymphocytes created by chimeric antigen receptor expression (CAR-T therapy).

CAR-T therapy is used in oncology: CAR-T cells can be specially adapted to the phenotypes of cancer cells present in a particular patient, thereby enhancing the immune response and showing increased selectivity and effectiveness. Anakinra is a recombinant human IL-1 receptor antagonist. This drug is used to treat rheumatoid arthritis, as well as hereditary cryopyrin-associated syndromes. In addition, anakinra is used "off-label" to stop the cytokine storm in CAR-T therapy, macrophage activation syndrome (MAS), including after ineffective tocilizumab therapy, as well as in secondary hemophagocytic lymphohistocytosis [67-69].

A systematic review and meta-analysis of 9 studies showed that anakinra reduces the need for invasive mechanical ventilation and the risk of mortality in hospitalized non-intubated patients compared to compared to standard treatment. However, confirmation of safety and efficacy requires an RCCT [70].

II. 4 INHIBITORS OF JANUS KINASES AND BRUTON TYROSINE KINASE

Janus kinase (JAK) inhibitors are suggested as a treatment for COVID-19 because they can prevent phosphorylation of key proteins involved in a signal transmission, which leads to the immune activation and inflammation (for example, cellular response to pro-inflammatory cytokines such as IL-6) [71]. Immunosuppression induced by this class of drugs has the potential to reduce the inflammation and associated immune pathologies seen in patients with COVID-19. In addition, JAK inhibitors, especially baricitinib, have a theoretical direct antiviral activity by interfering with viral endocytosis, potentially preventing the virus from entering susceptible cells and infecting them [72].

Currently, sufficient data are available only for the drug baricitinib, for other drugs in this class (for example, tofacitinib, fedratinib, ruxolitinib), as well as Bruton's tyrosine kinase inhibitors (acalabrutinib, ibrutinib, zanubrutinib), clinical trials are ongoing. On November 19, 2020, the FDA granted the emergency use authorization of baricitinib in combination with remdesivir in hospitalized adults and children aged 2 years and older with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) [73]. On December 14, 2020, a statement was issued regarding baricitinib, which included recommendations based on the results of ACTT-2 (Adaptive COVID-19 Treatment Trial 2).

This trial showed that baricitinib increased recovery time when administered in combination with remdesivir in patients who require additional oxygen support, but not invasive mechanical ventilation. However, a key limitation of ACTT-2 was the inability to assess the effect of baricitinib in addition to corticosteroids [74]. Next, the recent results of COV-BARRIER, a trial of baricitinib in hospitalized adults were

reviewed. COV-BARRIER included the patients with COVID-19 who, when were enrolled, required additional oxygen support, but not invasive mechanical ventilation. A study reported additional benefits of baricitinib when added to GCSs (with or without remdesivir) [75]. Currently, the drug is included in the national guidelines of some countries, which describe the criteria for its use.

II. 5 CORTICOSTEROIDS

The first drug with proven efficacy in improving clinical outcomes in hospitalized patients in the RECOVERY Trial was the GCS dexamethasone. Evaluation of the drug was also made in other trials, which results were similar [76]. Dexamethasone is currently used to treat hospitalized patients with COVID-19. Other corticosteroids (prednisone, methylprednisolone, and hydrocortisone) are supposed to be equivalent to the effective dosage of dexamethasone, but the available clinical trial results are contradictory, and some studies are in the active phase [77-81].

Of interest is the study of corticosteroids in outpatients to prevent the progression of COVID-19 course. To this end, a group of scientists from the UK initiated the STOIC (Steroids in COVID-19) Trial, which evaluated the efficacy of inhalation budesonide (in the form of a powder inhaler at a dose of 800 mcg twice a day) compared to conventional treatment. The study involved 146 subjects with moderate symptoms of COVID-19 who had developed symptoms about 7 days before, 73 of whom were assigned to the budesonide group and 73 to the standard treatment group.

The first endpoint of the assessment was a visit to the emergency department due to the worsening of COVID-19 course. The secondary endpoint of patient assessment was self-reporting of regression of clinical signs (resolution of symptoms) and viral disease symptoms, which were assessed using the Cold Questionnaire (CCQ-Clinical COPD Questionnaire) and the InFLUenza questionnaire (FLUPro); on body temperature, saturation, and viral load of SARS-CoV-2. The study was stopped prematurely after coming to a conclusion that the outcome of the study would not change with further inclusion of participants. According to the results of phase 2 of this study, an early use of inhalation budesonide at a high dose reduced the need for urgent medical care and reduced the duration of symptomatic disease [82]. However, despite the encouraging results, and despite the fact that the use of budesonide is included in the interim clinical guidelines of certain countries, it was found that the study had a number of limitations that could affect its outcome [83]. Further studies are needed to investigate the effects of inhalation corticosteroids in patients with COVID-19.

II. 6 ANTITHROMBOTIC THERAPY

The results of retrospective studies have provided evidence of the potential benefit of anticoagulant therapy at a therapeutic dose in patients with COVID-19, but these studies were too different in design to provide absolute indications for the use of certain methods [84-86]. A lot of questions: the management of outpatients, the administration of anticoagulant therapy after discharge with an initial severe course of infection, the dosage of drugs, the choice of the appropriate medicine remained and still remain in the gray zone. In addition, the description of several small series showed that the administration of thromboprophylaxis in an intermediate dose is associated with a high risk of complications in the form of bleeding [87, 88].

Thus, the need for well-developed and large-scale RCCTs of the efficacy and safety of anticoagulant treatment in patients with COVID-19 is obvious. At the beginning of the pandemic, a large number of RCCTs were initiated to study anticoagulant therapy for COVID-19, most of which are still in the active phase. The most large and well-known of them include the REMAP-CAP (Embedded Randomized Multifactorial Adaptive Platform for Community-acquired Pneumonia), ATTACC (Antithrombotic Therapy to Ameliorate Complications of COVID-19), ACTIV-4 (Anti-thrombotics for Adults Hospitalized With COVID-19), INSPIRATION (Intermediate-dose vs Standard Prophylactic Anticoagulation and Statin vs Placebo in ICU Patients With COVID-19), and also the study of heparinoid, that is the sulodexide drug. Some of these studies were presented as preliminary results, some as a full report, and a detailed description of the results will not be shown here.

Depending on the completion and results of clinical trials, the global clinical guidelines for the treatment and management of patients with COVID-19 are dynamically updated. As of June 2021, there is a preprint of

an article with the results of investigating aspirin in the RECOVERY Trial, which suggest that taking aspirin in combination with standard therapy is not associated with a reduction in mortality in hospitalized patients with COVID-19 [89].

At the moment, a centralized approach can be formed only for low-molecular-weight heparin. Due to the high thrombogenicity of COVID-19 in more severe cases of the disease, thromboprophylaxis with low-molecular-weight heparin should be administered to all hospitalized patients. However, an appropriate approach to thromboprophylaxis in outpatients, as well as the minimum effective dose for hospitalized patients, remains a topic of discussion.

Currently, thromboprophylaxis in outpatients with COVID-19, as well as planned thromboprophylaxis in patients after the discharge from hospital is not recommended. Given that the risk of thrombosis increases with the clinical deterioration, and that the proposed stages often overlap in clinical practice, conservative measures such as adequate mobilization and prevention of dehydration should be emphasized. A prophylactic dose of low-molecular-weight heparin in outpatients should be considered if there is an increased D-dimer, as well as inflammatory markers, since there is a risk of a rapid development of stage 2 coagulopathy. It should be noted that in this case it is important to assess the risks of bleeding. The same applies to patients who are severely ill, but for some reason have not been hospitalized. In patients who have recovered from COVID-19 and can be discharged from the hospital, long-term outpatient thromboprophylaxis is usually not recommended. However, for patients with a low risk of bleeding and a high risk of blood clots, therapy with low-molecular-weight heparin or direct oral anticoagulants may also be considered [90].

II.7 NON-DRUG TREATMENT

Non-drug treatments, with the exception of some related to oxygenation, do not yet have strong evidence in the fight against COVID-19. Most of the results are based on inaccurate estimates due to a small number of participants. Various forms of non-drug treatment are used to prevent severe complications: oxygen therapy, lying on the stomach, nitric oxide inhalation, passive immune therapy, and the infusion of mesenchymal stem cells (MSCs) [91].

It is assumed that MSCs can potentially be used as a therapy for COVID-19 and reduce the risk of its progression. The N. V. Sklifosovsky Research Institute for Emergency Medicine is searching for and developing innovative methods of respiratory support (helium-oxygen mixture, hyperbaric oxygenation, ECMO) for patients with COVID-19-caused pneumonia. A helium-oxygen mixture (t-He/O2) contributes to maintaining and improving the diffusion capacity of lungs [92-94]. When t-He/O2 inhalations are included in a standard therapy, the level of inflammatory markers decreases and the treatment efficacy increases; the synthesis of IgG and IgM antibodies is also stimulated, inducing the effect of "thermal vaccination". Currently, the response to t-He/O2 exposure is being studied in patients with CT signs of severe pneumonia. Preliminary data on the favorable effect of hyperbaric oxygenation sessions in "soft" modes included in complex therapy on the subjective state of patients and the dynamics of blood oxygen saturation have been published [92]. The ECMO technique is indicated in 3 cases: the respiratory support, cardiac support, and cardiorespiratory support. This method is particularly effective in groups of young patients with severe COVID-19 [93].

CONCLUSION

A large number of clinical studies are being conducted in relation to the search for a proven effective treatment strategy for COVID-19. The largest of them successfully exclude potentially ineffective methods of drug and non-drug therapy and provide data on those that improve the prognosis. While there is no targeted antiviral therapy, immunomodulatory methods and cytokine storm management come to the fore.

Dexamethasone was the first drug with proven efficacy in the prognosis of hospitalized patients. A recently completed trial of tocilizumab proved the drug's efficacy in hospitalized patients. Colchicine and monoclonal antibody preparations are currently showing promising results for outpatients.

Adequate thromboprophylaxis is of great importance in predicting the outcome of the disease, but it is always necessary to assess the risks. In the near future, many trials of various drugs and treatment methods are expected to be completed, which will allow us to successfully treat patients at various stages of the disease.

REFERENCES

1. Global Coronavirus COVID-19 Clinical Trial Tracker. Available at: https://www.covid-trials.org/ [Accessed June 05, 2021]
2. Randomised evaluation of COVID-19 therapy (RECOVERY). Available at: https://www.recoverytrial.net/files/protocol-archive/recovery-protocol-v6-0-2020-05-14.pdf [Accessed July 07, 2021]
3. Randomised Evaluation of COVID-19 Therapy (RECOVERY). Available at: https://www.clinicaltrials.gov/ct2/show/NCT04381936 [Accessed May 13, 2021] 13.05.2021)
4. RECOVERY Collaborative Group. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10274):605–612. PMID: 33545096 https://doi.org/10.1016/S0140-6736(21)00149-5
5. RECOVERY trial closes recruitment to colchicine treatment for patients hospitalised with COVID-19. Available at: https://www.recoverytrial.net/news/recovery-trial-closes-recruitment-to-colchicine-treatment-for-patients-hospitalised-with-covid-19 [Accessed July 07, 2021]
6. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet. 2021;397(10289):2049–2059. PMID: 34000257 https://doi.org/10.1016/S0140-6736(21)00897-7
7. Mrukowicz J, Rot M. Deksametazon pri tyazhelom techenii COVID-19. Available at: https://empendium.com/ru/chapter/B33.1394.54 [Accessed May 13, 2021]
8. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020;383(21):2030–2040. PMID: 33031652 https://doi.org/10.1056/NEJMoa2022926
9. Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on hydroxychloroquine, 5 June 2020. No clinical benefit from use of hydroxychloroquinein hospitalized patients with COVID-19. Available at: https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf [Accessed June 10, 2021]
10. Mrukowicz J, Gajowiec K. Issledovanie RECOVERY: lopinavir/ritonavir neeffektiven u patsientov s COVID-19 Available at: https://empendium.com/ru/chapter/B33.1394.65 [Accessed June 10, 2021]
11. RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2020;396(10259):1345-1352. PMID: 33031764 https://doi.org/10.1016/S0140-6736(20)32013-4
12. "Solidarity" clinical trial for COVID-19 treatments. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments [Accessed May 26, 2021]
13. Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Kum E, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ. 2020;370:m2980. PMID: 32732190 https://doi.org/10.1136/bmj.m2980
14. Corticosteroids for COVID-19. Living Guidance. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1 [Accessed June 12, 2021]
15. Therapeutics and COVID-19: living guideline, 20 November 2020. Available at: https://apps.who.int/iris/handle/10665/336729 [Accessed June 16, 2021]
16. Therapeutics and COVID-19: living guideline. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.1 [Accessed June 20, 2021]
17. Lloyd EC, Gandhi TN, Petty LA. Monoclonal antibodies for COVID-19. JAMA. 2021;325(10):1015. PMID: 33544136 https://doi.org/10.1001/jama.2021.1225
18. BMJ Best Practice. Coronavirus disease 2019 (COVID-19). Available at: https://bestpractice.bmj.com/topics/en-gb/3000201/emergingtxs#referencePop947 [Accessed June 12, 2021]
19. Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19-0 [Accessed June 23, 2021]
20. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Monoclonal Antibody Bamlanivimab. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab [Accessed June 21, 2021]
21. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA. 2021;325(7):632–644. PMID: 33475701 https://doi.org/10.1001/jama.2021.0202
22. Anti-SARS-CoV-2 Monoclonal Antibodies. Available at: https://www.covid19treatmentguidelines.nih.gov/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/ [Accessed June 13, 2021]
23. Phase 3 trial shows regen-cov™ (casirivimab with imdevimab) antibody cocktail reduced hospitalization or death by 70% in non-hospitalized covid-19 patients. Available at: https://investor.regeneron.com/news-releases/news-release-details/phase-3-trial-shows-regen-covtm-casirivimab-imdevimab-antibody [Accessed June 13, 2021]
24. Fact sheet for health care providers emergency use authorization (EUA) of casirivimab and imdevimab. Available at: https://www.fda.gov/media/143892/download [Accessed Jul 07, 2021]
25. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, un cóctel de anticuerpos neutralizantes, en pacientes ambulatorios con Covid-19. N Engl J Med. 2021;384(3):238–251. PMID: 33332778 https://doi.org/10.1056/NEJMoa2035002
26. EMA issues advice on use of REGN-COV2 antibody combination (casirivimab / imdevimab). Available at: https://www.ema.europa.eu/en/news/ema-issues-advice-use-regn-cov2-antibody-combination-casirivimab-imdevimab [Accessed June 14, 2021]
27. Anti-SARS-CoV-2 Antibody Products. Available at: https://www.covid19treatmentguidelines.nih.gov/anti-sars-cov-2-antibody-products/ [Accessed June 15, 2021]

28. ACTIV-3/TICO LY-CoV555 Study Group, Lundgren JD, Grund B, Barkauskas CE, Holland TL, Gottlieb RL, et al. A neutralizing monoclonal antibody for hospitalized patients with Covid-19. N Engl J Med. 2021;384(10):905–914. PMID: 33356051 https://doi.org/10.1056/NEJMoa2033130
29. EMA issues advice on use of regdanvimab for treating COVID-19. Available at: https://www.ema.europa.eu/en/news/ema-issues-advice-use-regdanvimab-treating-covid-19 [Accessed Jul 07, 2021]
30. Celltrion Develops Tailored Neutralising Antibody Cocktail Treatment with CT-P59 to Tackle COVID-19 Variant Spread Using Its Antibody Development Plat. Available at: https://www.celltrionhealthcare.com/en-us/board/newsdetail?modify_key=446 [Accessed June 15, 2021]
31. Celltrion's COVID-19 treatment candidate receives Korean MFDS Conditional Marketing Authorisation. Available at: https://www.celltrionhealthcare.com/en-us/board/newsdetail?modify_key=442 [Accessed June 15, 2021]
32. Clark E, Guilpain P, Filip IL, Pansu N, Le Bihan C, Cartron G, et al. Convalescent plasma for persisting COVID-19 following therapeutic lymphocyte depletion: a report of rapid recovery. Br J Haematol. 2020;190(3):e154–e156. PMID: 32593180 https://doi.org/10.1111/bjh.16981
33. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19-preliminary report. N Engl J Med. 2021;384(8):693–704. PMID: 32678530 https://doi.org/10.1056/NEJMoa2021436
34. Libster R, Marc GP, Wappner D, Coviello S, Bianchi A, Braem V, et al. Prevention of severe COVID-19 in the elderly by early high-titer plasma. https://doi.org/10.1101/2020.11.20.20234013 Available at: https://www.medrxiv.org/content/10.1101/2020.11.20.20234013v1 [Accessed Jul 07, 2021]
35. NIH halts trial of COVID-19 convalescent plasma in emergency department patients with mild symptoms. Available at: https://www.nih.gov/news-events/news-releases/nih-halts-trial-covid-19-convalescent-plasma-emergency-department-patients-mild-symptoms [Accessed June 16, 2021]
36. Bulanov AYu, Kostin AI, Petrikov SS, Lysenko MA, Popugaev KA, Fomina DS, et al. Convalescent plasma therapy of a new coronavirus infection: an experience of Moscow city hospitals. Russian Journal of Anaesthesiology and Reanimatology. 2020;(6–2):33–39. (in Russ.) https://doi.org/10.17116/anaesthesiology202006233
37. Immunoglobulins: SARS-CoV-2 Specific. Available at: https://www.covid19treatmentguidelines.nih.gov/anti-sars-cov-2-antibody-products/ivig---sars-cov-2/ [Accessed June 17, 2021]
38. Xie Y, Cao S, Dong H, Li Q, Chen E, Zhang W, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. J Infect. 2020;81(2):318–356. PMID: 32283154 https://doi.org/10.1016/j.jinf.2020.03.044
39. Hou X, Tian L, Zhou L, Jia X, Kong L, Xue Y, et al. Intravenous immunoglobulin-based adjuvant therapy for severe COVID-19: a single-center retrospective cohort study. Virol J. 2021;18(1):101. PMID: 34020680 https://doi.org/10.1186/s12985-021-01575-3
40. Zhang J, Yang Y, Yang N, Ma Y, Zhou Q, Li W, et al. Effectiveness of intravenous immunoglobulin for children with severe COVID-19: a rapid review. Ann Transl Med. 2020;8(10):625. PMID: 32566562 https://doi.org/10.21037/atm-20-3305
41. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–271. PMID: 32020029 https://doi.org/10.1038/s41422-020-0282-0
42. Table 2a. Remdesivir: Selected Clinical Data. Available at: https://www.covid19treatmentguidelines.nih.gov/tables/table-2a/ [Accessed June 10, 2021]
43. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19 – final report. N Engl J Med. 2020;383(19):1813–1826. PMID: 32445440 https://doi.org/10.1056/NEJMoa2007764
44. Fritz ML, Siegert PY, Walker ED, Bayoh MN, Vulule JR, Miller JR. Toxicity of bloodmeals from ivermectin-treated cattle to Anopheles gambiae s.l. Ann Trop Med Parasitol. 2009;103(6):539–547. PMID: 19695159 https://doi.org/10.1179/000349809X12459740922138
45. Omura S, Crump A. Ivermectin: panacea for resource-poor communities? Trends Parasitol. 2014;30(9):445–455. PMID: 25130507 https://doi.org/ 10.1016/j.pt.2014.07.005
46. Yang SNY, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Antiviral Res. 2020;177:104760. PMID: 32135219 https://doi.org/10.1016/j.antiviral.2020.104760
47. Arévalo AP, Pagotto R, Pórfido JL, Daghero H, Segovia M, Yamasaki K, et al. Ivermectin reduces coronavirus infection in vivo: a mouse experimental model. Sci Rep. 2021;11(1):7132. PMID: 33785846 https://doi.org/10.1101/2020.11.02.363242
48. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020;178:104787. PMID: 32251768 https://doi.org/10.1016/j.antiviral.2020.104787
49. Chaccour C, Abizanda G, Irigoyen-Barrio Á, Casellas A, Aldaz A, Martínez-Galán F, et al. Nebulized ivermectin for COVID-19 and other respiratory diseases, a proof of concept, dose-ranging study in rats. Sci Rep. 2020;10(1):17073. PMID: 33051517 https://doi.org/10.1038/s41598-020-74084-y
50. Schmith VD, Zhou JJ, Lohmer LRL. The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19. Clin Pharmacol Ther. 2020;108(4):762–765. PMID: 32378737 https://doi.org/10.1002/cpt.1889
51. Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, et al. SARS-CoV-2 y sepsis viral: observaciones e hipótesis. Lancet. 2020;395(10235):1517–1520. PMID: 32311318 https://doi.org/10.1016/S0140-6736(20)30920-X
52. van Echteld I, Wechalekar MD, Schlesinger N, Buchbinder R, Aletaha D. Colchicine for acute gout. Cochrane Database Syst Rev. 2014;(8):CD006190. PMID: 25123076 https://doi.org/10.1002/14651858.CD006190.pub2
53. Deftereos SG, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P, et al. Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized with Coronavirus Disease 2019: the GRECCO-19 Randomized Clinical Trial. JAMA Netw Open. 2020;3(6):e2013136. PMID: 32579195 https://doi.org/10.1001/jamanetworkopen.2020.13136
54. Rabbani AB, Parikh RV, Rafique AM. Colchicine for the Treatment of Myocardial Injury in Patients with Coronavirus Disease 2019 (COVID-19)—an Old Drug with New Life? JAMA Netw Open. 2020;3(6):e2013556. PMID: 32579190 https://doi.org/10.1001/jamanetworkopen.2020.1355

55. Tardif JC, Bouabdallaoui N, L'Allier PL, Gaudet D, Shah B, Pillinger MH, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. Lancet Respir Med. 2021;9(8):924–932. PMID: 34051877 https://doi.org/10.1016/S2213-2600(21)00222-8.
56. Vincent JL. COVID-19: it's all about sepsis. Future Microbiol. 2021;16:131–133. PMID: 33491491 https://doi.org/10.2217/fmb-2020-0312
57. Rosen DA, Seki SM, Fernández-Castañeda A, Beiter RM, Eccles JD, Woodfolk JA, et al. Modulation of the sigma-1 receptor–IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. Sci Transl Med. 2019;11(478):eaau5266. PMID: 30728287 https://doi.org/10.1126/scitranslmed.aau5266
58. Rafiee L, Hajhashemi V, Javanmard SH. Fluvoxamine inhibits some inflammatory genes expression in LPS/stimulated human endothelial cells, U937 macrophages, and carrageenan-induced paw edema in rat. Iran J Basic Med Sci. 2016;19(9):977–984. PMID: 27803785
59. Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients with Symptomatic COVID-19: A Randomized Clinical Trial. JAMA. 2020;324(22):2292–2300. PMID: 33180097 https://doi.org/10.1001/jama.2020.22760
60. Yoshikawa T, Hill T, Li K, Peters CJ, Tseng CT. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. J Virol. 2009;83(7):3039–3048. PMID: 19004938 https://doi.org/10.1128/JVI.01792-08
61. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–1062. PMID: 32171076 https://doi.org/10.1016/S0140-6736(20)30566-3
62. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506. PMID: 31986264 https://doi.org/10.1016/S0140-6736(20)30183-5
63. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis. 2020;71(15):769–777. PMID: 32176772 https://doi.org/10.1093/cid/ciaa272
64. Interleukin-6 Inhibitors: Selected Clinical Data Available at: https://www.covid19treatmentguidelines.nih.gov/tables/table-4b/ [Accessed Jun 17, 2021]
65. Ghosn L, Chaimani A, Evrenoglou T, Davidson M, Graña C, Schmucker C, et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021;3:CD013881. PMID: 33734435 https://doi.org/10.1002/14651858.CD013881
66. Rubin EJ, Longo DL, Baden LR. Interleukin-6 Receptor Inhibition in Covid-19 - Cooling the Inflammatory Soup. N Engl J Med. 2021;384(16):1564–1565. PMID: 33631064 https://doi.org/10.1056/NEJMe2103108
67. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P; CORIMUNO-19 Collaborative Group. Effect of Tocilizumab vs Usual Care in Adults Hospitalized with COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. 2021;181(1):32–40. PMID: 33080017 https://doi.org/10.1001/jamainternmed.2020.6820
68. CAR-T-kletki: Immunoterapiya opukholey. Available at: https://www.mybeckman.ru/resources/research-areas/immunotherapy/about-car-t-cells [Accessed Jun 17, 2021]
69. Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 Receptor Blockade Is Associated with Reduced Mortality in Sepsis Patients with Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. Crit Care Med. 2016;44(2):275–281. PMID: 26584195 https://doi.org/10.1097/CCM.0000000000001402
70. Monteagudo LA, Boothby A, Gertner E. Continuous Intravenous Anakinra Infusion to Calm the Cytokine Storm in Macrophage Activation Syndrome. ACR Open Rheumatol. 2020;2(5):276–282. PMID: 32267081 https://doi.org/10.1002/acr2.11135
71. Barkas F, Ntekouan SF, Kosmidou M, Liberopoulos E, Liontos A, Milionis H. Anakinra in hospitalized non-intubated patients with coronavirus disease 2019: a systematic review and meta-analysis. Rheumatology (Oxford). 2021 May 17:keab447. PMID: 33999135 https://doi.org/10.1093/rheumatology/keab447 Online ahead of print.
72. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clin Immunol. 2020;214:108393. PMID: 32222466 https://doi.org/10.1016/j.clim.2020.108393
73. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020;20(4):400–402. PMID: 32113509 https://doi.org/10.1016/S1473-3099(20)30132-8
74. Fact sheet for healthcare providers emergency use authorization (EUA) of baricitinib. Available at: https://www.fda.gov/media/143823/download [Accessed Jun 16, 2021]
75. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al.; ACTT-2 Study Group Members. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 2021;384(9):795–807. PMID: 33306283 https://doi.org/10.1056/NEJMoa2031994
76. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib in patients with COVID-19 infection: Results from the randomised, double-blind, placebo-controlled, parallel-group COV-BARRIER phase 3 trial. medRxiv 2021.04.30.21255934. https://doi.org/10.1101/2021.04.30.21255934 Available at: https://www.medrxiv.org/content/10.1101/2021.04.30.21255934v1 [Accessed Jul 07, 2021]
77. Corticosteroids: Selected Clinical Data. Available at: https://www.covid19treatmentguidelines.nih.gov/tables/table-4a/ [Accessed June 17, 2021]
78. Czock D, Keller F, Rasche FM, Häussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. Clin Pharmacokinet. 2005;44(1):61–98. PMID: 15634032 https://doi.org/10.2165/00003088-200544010-00003
79. Jeronimo CMP, Farias MEL, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, et al. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized with Coronavirus Disease 2019 (COVID-19; Metcovid): A Randomized, Double-blind, Phase IIb, Placebo-controlled Trial. Clin Infect Dis. 2021;72(9):e373–e381. PMID: 32785710 https://doi.org/10.1093/cid/ciaa1177

80. Dequin PF, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, et al. Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2020;324(13):1298–1306. PMID: 32876689 https://doi.org/10.1001/jama.2020.16761
81. Li Q, Li W, Jin Y, Xu W, Huang C, Li L, et al. Efficacy Evaluation of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Non-Severe COVID-19 Pneumonia: A Retrospective Cohort Study. Infect Dis Ther. 2020;9(4):823–836. PMID: 32880102 https://doi.org/10.1007/s40121-020-00332-3
82. Angus D C, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients with Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA. 2020;324(13):1317–1329. PMID: 32876697 https://doi.org/10.1001/jama.2020.17022
83. Ramakrishnan S, Nicolau DV Jr, Langford B, Mahdi M, Jeffers H, Mwasuku C, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. Lancet Respir Med. 2021;9(7):763-772. PMID: 33844996 https://doi.org/10.1016/S2213-2600(21)00160-0
84. San-Juan R, Fernández-Ruiz M, López-Medrano F, Aguado JM. Inhaled budesonide for early treatment of COVID-19. Lancet Respir Med. 2021;9(7):e58. PMID: 33991508 https://doi.org/10.1016/S2213-2600(21)00211-3
85. Lachant DJ, Lachant NA, Kouides P, Rappaport S, Prasad P, White RJ. Chronic therapeutic anticoagulation is associated with decreased thrombotic complications in SARS-CoV-2 infection. J Thromb Haemost. 2020;18(10):2640–2645. PMID: 33448631 https://doi.org/10.1111/jth.15032
86. Rivera-Caravaca JM, Núñez-Gil IJ, Vivas D, Viana-Llamas MC, Uribarri A, Becerra-Muñoz VM, et al. Clinical profile and prognosis in patients on oral anticoagulation before admission for COVID-19. Eur J Clin Invest. 2021;51(1):e13436. PMID: 33080051 https://doi.org/10.1111/eci.13436
87. Llitjos J-F, Leclerc M, Chochois C, Monsallier J-M, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. 2020;18(7):1743–1746. PMID: 32320517 https://doi.org/10.1111/jth.14869
88. Martin TA, Wan DW, Hajifathalian K, Tewani S, Shah SL, Mehta A, et al. Gastrointestinal Bleeding in Patients with Coronavirus Disease 2019: A Matched Case-Control Study. Am J Gastroenterol. 2020;115(10):1609–1616. PMID: 32796176 https://doi.org/10.14309/ajg.0000000000000805
89. Shah A, Donovan K, McHugh A, Pandey M, Aaron L, Bradbury CA, et al. Thrombotic and haemorrhagic complications in critically ill patients with COVID-19: a multicentre observational study. Crit Care. 2020;24(1):561. PMID: 32948243 https://doi.org/10.1186/s13054-020-03260-3
90. Horby PW, Pessoa-Amorim G, Staplin N, Emberson JR, Campbell M, Spata E, et al. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. medRxiv 2021.06.08.21258132 https://doi.org/10.1101/2021.06.08.21258132 Available at: https://www.medrxiv.org/content/10.1101/2021.06.08.21258132v1 [Accessed Jul 07, 2021]
91. Leentjens J, van Haaps TF, Wessels PF, Schutgens REG, Middeldorp S. COVID-19-associated coagulopathy and antithrombotic agents-lessons after 1 year. Lancet Haematol. 2021;8(7):e524–e533. PMID: 33930350 https://doi.org/10.1016/S2352-3026(21)00105-8
92. Pereira AA, de Oliveira Andrade A, de Andrade Palis A, Cabral AM, Lima Barreto CG, de Souza DB, et al. Non-pharmacological treatments for COVID-19: current status and consensus. Research on Biomedical Engineering. 2021;1–16. PMCID: PMC7809889 https://doi.org/10.1007/s42600-020-00116-1 [Epub ahead of print]
93. Zhuravel' SV, Gavrilov PV, Kuznetsova NK, Utkina II, Talyzin MA, Aleksandrova VE. Case report: thermal helium in the treatment of coronavirus pneumonia caused by new coronavirus infection COVID-19 (SARS-CoV-2). Bulletin of the Medical Institute "REAVIZ" (Rehabilitation, Doctor and Health). 2021;(1):5–10. (In Russ.) https://doi.org/10.20340/vmi-rvz.2021.1.COVID.1
94. Levina OA, Evseev AK, Shabanov AK, Kulabukhov VV, Kutrovskaya NYu, Goroncharovskaya IV, et al. The Safety of Hyperbaric Oxygen Therapy in the Treatment of Covid-19. Russian Sklifosovsky Journal Emergency Medical Care. 2020;9(3):314–320. https://doi.org/10.23934/2223-9022-2020-9-3-314-320
95. Shogenova LV, Varfolomeev SD, Bykov VI, Tsybenova SB, Ryabokon AM, Zhuravel SV, et al. Effect of thermal helium-oxygen mixture on viral load in COVID-19. Pulmonologiya. 2020;30(5):533–543. https://doi.org/10.18093/0869-0189-2020-30-5-533-543

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