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Coronavirus Disease 19 (COVID-19) Pharmacologic Treatment: Where Are We Now?

Farmakološko liječenje koronavirusne bolesti 19 (COVID-19): gdje smo sada?

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Summary

Since the first cases of COVID-19 were reported from China the disease became pandemic within a few months. The viral genome was sequenced soon after the outbreak of COVID-19 which enabled development of diagnostic tests and therapeutic options. As the knowledge of SARS-CoV-2 virology increased, many potential drugs appeared. At this moment (January 12th 2021), 4426 studies of COVID-19 are registered, and more than 2680 studies are investigating therapeutic options. This is a short narrative review of currently available evidence on pharmacological treatment of COVID-19.

Sažetak

U roku nekoliko mjeseci od pojave prvih slučajeva COVID-19 u Kini, bolest je poprimila pandemijske razmjere. Virusni genom je sekvencioniran ubrzo nakon pojave COVID-19 što je omogućilo razvoj dijagnostičkih testova i terapije. Kako su pristizala saznanja o samom virusu SARS-CoV-2, pojavljivali su se razni potencijalni lijekovi. U ovom trenutku (12. siječnja 2021.) registrirano je 4426 studija o COVID-19, a više od 2680 studija se bavi istraživanjem terapijskih opcija. U ovom preglednom radu prikazana su sadašnja saznanja o farmakološkom liječenju COVID-19.

Introduction

The pandemic novel coronavirus disease 2019 (COVID-19) rapidly spread worldwide since the beginning in Wuhan, China in the end of December 2019[1]. Soon after the outbreak in Wuhan has been recognized, a causative agent was discovered. The virus was firstly named a novel coronavirus, 2019-nCoV, but it was soon renamed to SARS-CoV-2[2]. It is a single-stranded RNA virus of approximately 27–32 kb and the seventh member of the family Coronaviridae that causes illness in humans[2,3]. The viral genome was sequenced soon after the outbreak of COVID-19 which enabled development of diagnostic tests and therapeutic targets[2]. Until January 3rd, a total of 83 326 479 COVID-19 cases and 1 831 703 deaths were reported globally[4]. As a result of pandemic's profound impact on healthcare systems worldwide, many clinical trials assessing the efficacy of different therapeutic options emerged. Until April 24th, over 500 clinical trials on COVID-19 treatment were registered[5] and at this moment (January 12th 2021) 2680 studies of treatment are registered on Clinicaltrials.gov. There is no evidence of benefits of prophylactic therapy and it will not be discussed here[6]. This review will give an overview of current knowledge of pharmacologic treatment of COVID-19.

Antiviral drugs

Remdesivir – possible benefit in some patients

Remdesivir (GS-5734) is a novel nucleotide analogue prodrug in a parenteral form. Currently, it is the only antiviral drug against SARS-CoV-2 confirmed to be effective in clinical trials. It undergoes metabolic conversion in cells to active metabolite which inhibits viral RNA-dependent RNA polymerase[7]. Remdesivir was discovered during the screening process for drugs with activity against Coronaviridae and Flaviviridae and showed activity against SARS-CoV-2 in vitro[6-8]. The pharmacokinetics of remdesivir was evaluated in phase one clinical trials on Ebola[7]. Serum and intracellular half-life of remdesivir are 0.9 and 40 hr, re-

spectively, intravenous doses between 3 mg and 225 mg were well tolerated and it demonstrated linear pharmacokinetics within the dose range[6]. A renal adjustment dose has not been evaluated, however, remdesivir is not recommended for patients with an estimated glomerular filtration rate < 30 mL/min. After multiple administrations of remdesivir, aspartate aminotransferase (AST) and ALT elevation have been observed[6]. There are no dosage adjustments for baseline hepatic impairment, however, if hepatotoxicity (alanine aminotransferase [ALT] >10 times the upper normal limit or ALT elevation and signs or symptoms of liver inflammation) develops during treatment remdesivir should be discontinued. Remdesivir is not considered genotoxic[7]. Currently remdesivir is used as a single 200 mg dose, followed by 100 mg daily. The total duration of therapy is 5 or 10 days, depending on the response and severity of disease. If there is no clinical improvement or progression of disease a 10-day course is recommended[9, 10]. A randomized, double-blind, placebo-controlled, multicentre trial in China, which involved 237 adults with confirmed SARS-CoV-2 infection and radiologically confirmed pneumonia showed no difference in time to clinical improvement among patients who received remdesivir and patients who received placebo (hazard ratio (HR) 1.23 [95% CI 0.87–1.75]) and mortality at day 28 was similar (14% vs 13%, respectively) (Table 1)[11]. However, patients (with symptom duration of 10 days or less) who received remdesivir had a faster time to clinical improvement (HR 1.52 [95% CI 0.95–2.43]), although not statistically significant[11]. In this trial concomitant use of lopinavir–ritonavir, interferons, and corticosteroids were not permitted[11]. The final results from randomized, double-blind, placebo-controlled trial NIAID ACTT-1 on 1062 Covid-19 patients with evidence of lower respiratory tract involvement showed that 541 patients treated with remdesivir intravenously (200 mg on day 1, followed by 100 mg daily for 9 days) had a shorter time to recovery compared to placebo group (median 10 days *vs* 15 days, retrospectively, p<0.001) (Table 1)[12]. Another randomized, open-label trial which included hospitalized Covid-19 patients with pneumonia showed no difference in efficacy between a 5 day and a 10-day treatment with remdesivir, although it was shown that a 10-day course may be of benefit for patients who progressed to mechanical ventilation[13]. In the large open-labelled randomized Solidarity trial 2743 patients were assigned to the remdesivir group and 2708 to the control arm. There was no difference in mortality between patients who received remdesivir versus controls (Rate ratio, 0.95 (95% CI, 0.81–1.11))[14]. In a double-blind, randomized, placebo-controlled trial remdesivir given with a Janus kinase inhibitor (baricitinib) was compared to remdesivir alone. Faster recovery was observed in the remdesivir plus baricitinib group of patients (Table 1)[15]. Serious adverse events to remdesivir were not frequently observed in randomized trials. In the NIAID ACTT-1 study adverse reactions leading to treatment discontinuation were recorded in 2% of patients receiving remdesivir and in 3% receiving placebo[12]. In the study by Goldman et al.[13] the most common adverse events were nausea (9%), worsening respiratory failure (8%), elevated ALT (7%), and constipation (7%).

Favipravir- more data needed

Favipravir (T705) is an oral prodrug of a purine nucleotide which inhibits the RNA-dependent RNA polymerase and induces lethal RNA transversion mutations[16]. Safety and efficacy of favipiravir has been confirmed in influenza and it is currently available for the treatment of influenza in Japan[6, 17]. Previous clinical trials conducted during the Ebola outbreak suggested that favipiravir is active in Ebola patients with high viral load[16]. Studies on the healthy subjects showed a short half-life time of favipravir of 2–5.5 hours[6, 17]. Dosing varies and depends on the type of infectious disease; higher doses should be considered for the treatment of COVID-19[6]. Optimal dose and duration of treatment is still not known and currently used dosage schemes are: 1600 mg every 12 hours first day (q12h), followed by 600 mg q12h for a total duration of 7 to 14 days[18]. Another clinical trial (NCT04303299) is using a dose of 2400 mg every 8 hours for 2 doses, followed by a dose of 1200 mg every 8 hours on day 1, followed by maintenance dose of 1200 mg twice daily. No differences in clinical outcomes were found between favipiravir plus inhaled interferon beta-1b *vs.* hydroxychloroquine in 89 adults hospitalized due to moderate or severe COVID-19 pneumonia[19]. A small open label clinical trial compared the effects of favipiravir plus interferon (IFN)-α by aerosol inhalation (N=35) with lopinavir/ritonavir plus IFN-α by aerosol inhalation (N=45)[18]. In the favipravir arm, a shorter viral clearance (median 4 days *vs* 9 days, p<0.001), improvement in chest imaging (91.43% *vs* 62.22%, p=0.004) and fewer adverse reactions were observed[18]. In a prospective, randomized, multicentre study favipiravir (n = 120) was compared to arbidol (n = 120) for treatment of COVID-19 patients[20]. There were no differences in clinical recovery rate at day 7, but favipiravir had shorter time to relief for pyrexia (difference: 1.70 days, p<0.0001) and cough (difference: 1.75 days, p<0.0001)[20]. Randomized placebo-controlled trials evaluating favipravir as a treatment of COVID-19 are underway (NCT04464408,

NCT04336904, NCT04425460, NCT04600895). Most common adverse events reported in the WHO pharmacovigilance database suspected to be caused by the favipravir included increased hepatic enzymes, nausea, vomiting, tachycardia, and diarrhoea. Severe adverse events included blood and lymphatic, cardiac and hepatobiliary disorders, injury poisoning, and procedural complications[21]. Currently, there is not enough data to recommend its use for patients with renal impairment or patients on haemodialysis while in patients with hepatic impairment adjustment of dosage should be considered[22].

Chloroquine/hydroxychloroquine - Efficacy unproven, adverse events concern

Soon after emergence of the new virus, in vitro studies have reported *in vitro* inhibition of SARS-CoV-2 virus by both chloroquine and hydroxychloroquine, with hydroxychloroquine potentially having more potent antiviral activity[23]. Current literature data are controversial and contradictory, suggesting limited or no benefit of chloroquine and hydroxychloroquine for COVID-19 patients, with concerns about adverse events. At the time of writing this paper, The National Institutes of Health recommends against the use of chloroquine or hydroxychloroquine, with or without azithromycin, for COVID-19 treatment[9]. Initial small clinical reports seemed promising, but most lacked proper methodology. For example, the French study involving 36 adults with COVID-19 reported that the use of hydroxychloroquine (200 mg three times per day for 10 days) was associated with a higher rate of undetectable SARS-CoV-2 RNA in nasopharyngeal specimens at day 6 compared with no specific treatment (70 *vs* 12.5 %)[24]. However, it was a non-randomized, open-label, underpowered study with other methodological issues. On the other hand, in an observational study of 1446 patients hospitalized in New York, 811 patients were treated with hydroxychloroquine, which was associated with a higher risk of intubation or death (HR 2.37). In the multivariable analysis, this association was not significant (HR [95% CI 0.82-1.32])[25]. This study had serious limitations as well, such are disproportional differences between the patient groups and lack of randomization. In a retrospective cohort study on 7914 COVID-19 patients, treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality[26]. Concerns about serious side effects have been raised as well, including cardiotoxicity. The observational study by Mahévas et al. from France reported electrocardiographic modifications that required discontinuation of treatment in eight patients (10%) in the treatment group[27]. In the study by Borba et al, QTc dynamics was evaluated and QTc increased to >500 milliseconds in 18.9% high-dose recipients and 11.1% low-dose recipients. Two high-dose chloroquine recipients developed VT, but no Torsade de pointes was reported[28]. The trial which compared two doses of chloroquine (600 mg CQ twice daily for 10 days *vs* 450 mg twice daily on day 1 and once daily for 4 days) for COVID-19, was stopped early because of a higher mortality rate in the high-dose group (39.0% versus 15.0% in the low-dosage group at day 13) after enrolment of 81 participants out of a predefined sample size of 440[28].

The most recent and high-quality evidence come from two randomized-controlled trials (RECOVERY and SOLIDARITY) that suggest little to no benefit of treatment of COVID-19 with hydroxychloroquine[14, 29]. The Executive group of the WHO SOLIDARITY trial enrolled 11,330 adults and reported death at 28-day in 104 of 947 patients receiving hydroxychloroquine and in 84 of 906 receiving standard-of-care (RR 1.19; 95% CI, 0.89 to 1.59; P = 0.23)[14]. Similarly, in the RECOVERY trial the patient's death by 28 days occurred in 27% patients in the hydroxychloroquine group and in 25% in the standard-of-care group (RR 1.09; 95% confidence interval [CI], 0.97 to 1.23; P=0.15), with consistent results in subgroups of patients. A small excess of cardiac deaths (0.4%) was noted but the incidence of new major cardiac arrhythmia among the patients who received hydroxychloroquine was absent[29]. Some groups examined the use of the hydroxychloroquine in mild-to-moderate COVID-19 patients. In one of those studies conducted in the United States and Canada, hydroxychloroquine (800 mg followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 days) or placebo were administered to non-hospitalized adults. At 14 days, change in symptom severity was similar in both groups (difference: relative, 12%; absolute, −0.27 point [95% CI, −0.61 to 0.07 point]; $P = 0.117$), while 24% of participants receiving hydroxychloroquine had ongoing symptoms compared with 30% receiving placebo ($P = 0.21$). Medication adverse effects were reported in 43% of participants receiving hydroxychloroquine versus 22% in placebo group ($P < 0.001$)[30]. Another group conducted a multicentre, randomized controlled trial in mild-to-moderate hospitalized patients testing use of hydroxychloroquine alone (400 mg twice daily for 7 days) and with azithromycin (400 mg hydroxychloroquine twice daily plus 500 mg azithromycin once daily for 7 days). Compared with standard-of-care, hydroxychloroquine alone (OR, 1.21; 95% CI, 0.69 to 2.11; P=1.00) or hydroxychloroquine plus azithromycin (OR, 0.99; 95% CI, 0.57 to 1.73; P=1.00)

did not differ in clinical benefit at 15 days. Adverse events, namely prolongation of the QTc interval and elevation of liver-enzyme levels were more frequent in patients receiving hydroxychloroquine, alone or with azithromycin, than in controls[31]. Administration of hydroxychloroquine as post-exposure prophylaxis after high- or moderate-risk exposure to COVID-19 did not prevent illness as well[32].

Ribavirin - Clinical benefit not demonstrated

Ribavirin is a guanosine analogue with a broad-spectrum antiviral activity. Interest in it grew after the emergence of SARS-CoV-2, however, relevant clinical data on its effectiveness and use in SARS-CoV-2 patients is limited. Most of the data comes from research on SARS-CoV-1; for example, a study of ribavirin given in combination with lopinavir/ritonavir for the treatment of patients with acute respiratory distress syndrome (ARDS) *vs* lopinavir/ritonavir alone[33]. *In vitro* report of ribavirin effectiveness against SARS-CoV-2 revealed that the required effective concentration is quite high (EC_{50} = 109.50 μM), rising concerns about side effects[8]. In the meantime, the first clinical trial on COVID-19 treatment with ribavirin in combination with interferon beta-1b and/or lopinavir–ritonavir has been published[34]. Patients were treated either with triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin, or lopinavir–ritonavir and ribavirin, while the control group received lopinavir–ritonavir. The results showed reduction in duration of RT-PCR positivity and viral load accompanied with clinical improvement and shorter duration of hospital stay. However, due to the combination treatment, it cannot be determined which of the compounds contributed the most to the outcomes[34]. In a recently published retrospective cohort study ribavirin versus standard therapy was tested in severe COVID-19. The negative conversion time of RT-PCR in the ribavirin group was 12.8 ± 4.1 days compared with 14.1 ± 3.5 days in the control group (P = 0.314). Of 115 patients in the ribavirin group, 17.1% died compared with 24.6% in the control group (P = 0.475). Adverse effects were similar between the two groups[35]. In another small study of 62 patients with severe COVID-19, the researchers tested sofosbuvir/daclatasvir or ribavirin. All participants also received the recommended standard treatment (at that time lopinavir/ritonavir and hydroxychloroquine). The mortality in the sofosbuvir/daclatasvir group was 6% *vs* 33% in the ribavirin group[36]. On the other hand, a small randomized trial testing efficacy of sofosbuvir plus daclatasvir in combination with ribavirin showed no difference in the number of deaths between the groups (0 *versus* 3, P = 0.234)[37].

Lopinavir/ritonavir - Clinical benefit not demonstrated

Lopinavir/ritonavir is a combined protease inhibitor and booster, primarily used for the treatment of HIV infection. Lopinavir showed antiviral effect against SARS-CoV and MERS-CoV and it was recently showed that it inhibits replication of SARS-CoV-2[38]. In the report of pharmacokinetic data of lopinavir and ritonavir in COVID-19 patients (400 mg of lopinavir and 100 mg of ritonavir twice daily for 3 to 10 days before analysis) it was shown that approximately 60- to 120-fold higher concentrations are required to reach the assumed EC50[39]. In the early pandemic, reports of treatment with lopinavir/ritonavir were mostly small retrospective, non-randomized studies and case reports, which made definitive conclusions about benefit for COVID-19 patients difficult[6]. In the RECOVERY study on hospitalized patients with COVID-19, lopinavir–ritonavir was not associated with reductions in 28-day mortality, length of hospital stay, or risk of progression to invasive mechanical ventilation or death[40]. In a randomized control trial on 199 COVID-19 patients, lopinavir/ritonavir (400/100 mg twice daily for 14 days) also showed no significant benefit than standard care in terms of the time to clinical improvement (HR 1.31 [95%CI, 0.95 to 1.80]), mortality at 28 days (19.2% *vs* 25.0%, respectively; 95% CI, −17.3 to 5.7), and viral RNA was detectable in similar percentages of patients at various times[41]. However, this study was underpowered and included mainly patients with severe infection, and the median time from symptom onset to treatment was 13 days[42]. Lopinavir and ritonavir are inhibitors of the P450 cytochrome and they have significant drug-drug interactions and adverse drug events. Common reported adverse effects are gastrointestinal (diarrhoea, nausea), hepatotoxicity, blood glucose disorders and rash[43]. In the study by Cao et al. lopinavir/ritonavir was stopped early in 13.8% of patients due to adverse events, but percentages of patients who reported adverse events were similar in lopinavir-ritonavir group and in the standard-care group (48.4% *vs* 49.5%, respectively)[41]. National Institutes for Health and Infectious Diseases Society of America Guidelines recommend against using lopinavir/ritonavir to treat COVID-19, except in a clinical trial[9, 10]. In silico studies identified some other potential protease inhibitors for treatment of COVID-19 and trials of darunavir/cobicistat for treatment of COVID-19 (NCT04252274) is ongoing in Shangai, China[44]. However, the manufacturer of darunavir (Johnson & Johnson) has warned that there is no clinical nor pharmacological evidence to support the inclusion of darunavir-based treatment in guidelines for COVID-19, nor are there published

data on the safety and efficacy profile of darunavir in treatment of COVID-19[45, 46].

Immune based therapy

Convalescent plasma- more data needed

The Food and Drug Administration has approved the emergency use of convalescent plasma for the treatment of COVID-19[47]. Since then, many patients received convalescent plasma, particularly in the USA where it has been estimated that > 70 000 patients received convalescent plasma[9]. However, there is still little data from randomized trials published in peer-reviewed journals regarding the use of convalescent plasma. Four randomized trials have been peer-reviewed and published as of January 2021, of which only one showed clinical benefits[48] (Table 1). In this double-blind randomized study convalescent plasma was given to patients older than 75 years of age, regardless of concurrent comorbidity, or between 65 and 74 years of age with at least one comorbidity. Convalescent plasma with high titres (IgG titre greater than 1:1000 against SARS-CoV-2 spike protein) was given within 72 hours after onset of symptoms. Of 80 patients who were given convalescent plasma 13 (16%) progressed to severe disease whereas in the placebo group 25 (31%) of 80 progressed (relative risk reduction of 48%). Administration of convalescent plasma is not without adverse effects. In a published report of a convenience sample of 20000 patients, 13 deaths and 83 nonfatal serious events (37 circulatory overload events, 20 lung injury events, and 26 severe allergic reactions) have been reported as possibly or probably related to convalescent plasma[49]. There were also thromboembolic or thrombotic events (n=87; <1%), and cardiac events (n=680, ~3%) reported.

Monoclonal antibodies - more data needed

Antibodies with high and broad neutralizing capacity, particularly those that bind to the receptor binding domain of the spike protein block the entry of SARS-CoV-2 virus into target cells and as such are promising agents for both prophylaxis and treatment of COVID-19. The Food and Drug Administration has granted emergency approval for two formulations of monoclonal antibodies for the treatment of COVID-19: bamlanivimab and the casirivimab/imdevimab (REGN-COV2) cocktail. Both monoclonal antibody formulations showed a reduction of SARS-CoV-2 viral load from the nasopharyngeal swabs in randomized double blind clinical trials[50, 51].

LY-CoV555 (also known as bamlanivimab) did not show any efficacy compared to best standard of care (treatment with remdesivir was also given) in a recently published randomized double-blind trial including hospitalized patients who had symptoms attributable to COVID-19 of 12 or less days. There was no effect of bamlanivimab on clinical improvement compared to placebo (OR 0.85, 95% CI 0.56 to 1.29). There was also no benefit it terms of outcome (a composite endpoint of death, serious laboratory or clinical adverse events), being 19% in the bamlanivimib group and 14% in the placebo group[52]. There is currently very little data on the clinical effectiveness of REGN-COV2 cocktail, results of randomized trials are expected in the near future.

Interleukin inhibitors – more data needed

Severe organ damage, particularly lung damage, is probably caused by an excessive immune response and „cytokine storm". This can result in increased alveolar-capillary gas exchange and lead to hypoxemia. Interleukins are mediators of this immune response and in a study from Wuhan, China interleukin-6 (IL-6) was elevated in COVID-19 non survivors compared with survivors[53].

Clinical trials of several monoclonal antibodies against IL-6 are underway, some of which have already been published. Tocilizumab, a monoclonal antibody IL-6 receptor antagonist is approved for treating rheumatoid arthritis and cytokine release syndrome[6]. In a case series of 20 patients with severe or critical COVID-19 treated with tocilizumab, 75% had better oxygenation within 5 days, in 90.5% CT scans improved and the defervescence achieved on the first day after the treatment[54]. Another retrospective study on 25 patients treated with tocilizumab and investigational antiviral drugs showed a decline in inflammatory markers, reduced ventilatory support requirements and radiological improvement[55]. Initial nonrandomized studies were promising as well. One meta-analysis of nonrandomized studies reported that the tocilizumab group had lower mortality than the control group. The risk ratio was 0.27 (95% CI, 0.12–0.59) and the risk difference was 12% (95% CI, 4.6%–20%) for tocilizumab[56].

Randomized clinical trials were not as promising. An open-label, randomized clinical trial of 131 non-ICU patients with COVID-19 and pneumonia requiring oxygen support compared treatment with tocilizumab *versus* standard care. Though tocilizumab did not reduce World Health Organization 10-point Clinical Progression Scale (WHO-CPS) scores lower than 5 at day 4, in the tocilizumab group 12% (95% CI −28% to 4%) fewer patients needed non-invasive ventilation (NIV), mechanical ventilation (MV), or died by day 14. No difference on day 28 mortality was found[57].

Another randomized, double-blind, placebo-controlled trial involving patients with confirmed severe SARS-CoV-2 infection who received tocilizumab and controls, was inconclusive. The hazard ratio for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% CI, 0.38 to 1.81; P=0.64), and the hazard ratio for disease worsening was 1.11 (95% CI, 0.59 to 2.10; P=0.73)[58]. Other randomized clinical trial reported lack of benefit of tocilizumab treatment for COVID-19 as well[59]. Multiple RCTs are currently underway, comparing tocilizumab and corticosteroids (NCT04345445, NCT04377503), combining tocilizumab, hydroxychloroquine and azithromycin (NCT04332094) and tocilizumab with favipravir (NCT04310228).

Sarilumab is an IL-6 antagonist being investigated for treatment of COVID-19 in several studies (NCT04357808, NCT04357860, NCT04324073). However, in the Phase 3 analysis, sarilumab had no notable benefit on clinical outcomes in the severe and critical groups, versus placebo[60].

Some groups tested if anakinra, a recombinant IL-1 receptor antagonist, might help to neutralize the hyperinflammatory state. Initial small cohort study in France with 52 consecutive patients included in the anakinra group and 44 historical patients as controls was promising. Admission to the ICU for invasive mechanical ventilation or death occurred in 13 (25%) patients in the anakinra group and 32 (73%) patients in the historical group (HR 0.22 [95% CI 0.11 to 0.41); p=0.0002)[61]. On the other hand, in a recently published cohort study of critically ill COVID-19 patients, no significant differences in thrombocyte counts, PaO_2/FiO_2 ratio, or total SOFA score were observed in the anakinra group[62]. Randomized control trials are underway (NCT04603742, NCT04643678, NCT04443881).

Corticosteroids - benefit demonstrated

The benefit of corticosteroid use in septic shock is due to alleviating the host immune response and thus preventing the damage to organism. The idea for use of corticosteroids in COVID-19 patients was to decrease the host inflammatory responses in the lungs[6]. However, results from studies of corticosteroids in patients with SARS and MERS showed no improved survival and indicated an association with later viral clearance from the respiratory tract and blood and high rate of complications[6]. In the RECOVERY study 2104 COVID-19 patients were assigned to receive dexamethasone (6 mg once daily oral or intravenous for 10 days) and 4321 received usual care. The 28-day mortality was lower in the dexamethasone group *vs.* the usual care group (22.9% *vs.* 25.7%, age-adjusted rate ratio, 0.83; 95% CI, 0.75 to 0.93; P<0.001). In patients treated with dexamethasone the incidence of death was lower than in the usual care group in those on invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94). There was no statistically significant difference among patients who did not receive oxygen at randomization however, there was numerically a worse outcome in those who received dexamethasone (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55)[63]. This study had also some limitations: lack of data on viral clearance and the level of oxygen support[64]. In a study of 149 critically ill patients with COVID-19 and acute respiratory failure, low-dose hydrocortisone vs. placebo, did not significantly reduce treatment failure (defined as death or persistent respiratory support) at day 21 (difference of proportions, -8.6% [95.48% CI, -24.9% to 7.7%]; P = 0.29)[65]. In the CoDEX randomized clinical trial of patients with moderate or severe ARDS due to COVID-19, use of intravenous dexamethasone (20 mg daily for 5 days, then 10 mg daily for 5 days or until ICU discharge) plus standard care compared with standard care alone resulted in a significant increase in the number of ventilator-free days over 28 days (difference, 2.26; 95% CI, 0.2-4.38; P = 0.04)[66]. In a randomized placebo-controlled study from Brazil 416 patients with suspected or confirmed COVID-19 pneumonia received a short course methylprednisolone (0.5 mg/kg twice daily for 5 days) or placebo. There was no difference between the groups in mortality at day 7, 14 and 28-day or in the need for mechanical ventilation. The 28-day mortality rate in patients >60 years old was lower in the methylprednisolone group vs. placebo group (46.6% vs. 61.9% of participants, respectively; HR 0.63; 95% CI, 0.41–0.98; P = 0.039)[67]. In a retrospective study of 201 patients with COVID-19 from China, among patients with ARDS (26.4%), treatment with methylprednisolone decreased the risk of death (HR, 0.38 [95% CI 0.20-0.72])[68]. In 11/31 COVID-19 patients in China who received corticosteroids the analysis showed no association between corticosteroid treatment and virus clearance time (HR, 1.26 [95% CI 0.58-2.74]), hospital length of stay (HR 0.77 [95% CI, 0.33-1.78]), or duration of symptoms (HR 0.86 [95% CI, 0.40-1.83])[69]. A meta-analysis that evaluated the efficacy of systemic corticosteroids (dexamethasone, hydrocortisone, and methylprednisolone) in 1703 critically ill patients with COVID-19 compared with usual care or placebo, treatment with corticosteroids was associated with lower 28-day all-cause mortality (summary OR, 0.66 [95%

CI, 0.53-0.82], P < .001)[70]. The fixed-effect summary OR for the association with all-cause mortality for dexamethasone was 0.64 (95% CI, 0.50–0.82; P < 0.001) in three trials with 1282 patients[70]. RCTs investigating the potential of methylprednisolone (NCT04673162, NCT04343729, NCT04438980), dexamethasone (NCT04344730, NCT04640168) and hydrocortisone (NCT04348305, NCT04366115) are now in different phases. National Institutes for Health Guidelines and Infectious Diseases Society of America Guidelines do not recommend the use of dexamethasone in patients who do not require supplemental oxygen, but it is recommended in those who need supplemental oxygen through nasal cannula, masks, or high flow device, non-invasive or invasive mechanical ventilation or ECMO. Recommended dose is 6 mg PO or IV once daily for 10 days or until hospital discharge[9,10].

Baricitinib - more data needed

Baricitinib is an oral Janus kinase (JAK) inhibitor approved by the FDA for the treatment of rheumatoid arthritis. The FDA issued an Emergency Use Authorization in November 2020 for the use of baricitinib with remdesivir in hospitalized COVID-19 patients aged ≥2 years who require supplemental oxygen, invasive mechanical ventilation, or ECMO[9]. A randomized placebo-controlled study of 1033 patients treated with baricitinib plus remdesivir or placebo plus remdesivir showed that patients treated with baricitinib plus remdesivir recovered faster (median, 7 days *vs.* 8 days; rate ratio for recovery, 1.16; 95%CI, 1.01 to 1.32; P=0.03). Time to recovery among patients on non-invasive ventilation or high-flow oxygen was 10 days in baricitinib plus remdesivir *vs.* 18 days in the control group (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). The 28-day mortality was 5.1% in the combination group and 7.8% in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09)[15]. In NIH treatment guidelines baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized, non-intubated patients who require oxygen supplementation is recommended in the rare circumstances where corticosteroids cannot be used[9].

Ivermectin - more data needed

Ivermectin is an antiparasitic drug approved for the treatment of onchocerciasis, helminthiases, and scabies[9]. It was shown to be effective in vitro against the viruses Zika, dengue, HIV, and yellow fever[9]. It is effective SARS-CoV-2 inhibitor in vitro[71]. Yang et al. showed ability of ivermectin to target the host importin α/β1 nuclear transport proteins responsible for intracellular transport process which is altered by viruses to enhance infection[72]. However, the clinical data on the use of ivermectin are limited. In a study from Egypt which included 400 patients with confirmed COVID-19 patients with mild/moderate and severe COVID-19 who were treated with ivermectin plus standard of care (azithromycin, vitamin C, zinc, lactoferrin, acetylcysteine and prophylactic or therapeutic anticoagulation) had lower mortality rate (0% and 2%, respectively) in comparison to patients who received hydroxychloroquine and standard of care (4% and 20%, respectively). Also, they had substantial improvement in laboratory parameters one week after treatment (p<0.001)[73]. A retrospective study of 280 patients hospitalized due to COVID-19 showed lower mortality in patients who were treated with ivermectin (15.0% *vs.* 25.2%; OR, 0.52; 95% CI, 0.29-0.96; P = 0.03). However, patients in both groups (ivermectin and no-ivermectin) also received hydroxychloroquine, azithromycin, or both, and those who received ivermectin were also more likely to receive corticosteroids[74]. In a study of 180 mild to severe COVID-19 patients from Iranian authors a shorter hospital stay was observed in ivermectin treated groups compared to two groups treated with common regimen (hydroxychloroquine) (P=0.006 and P=0.025, respectively). The lowest mortality rate (0%) and hospital stay (median: 5 days) was recorded in patients treated with a single dose of ivermectin (400 mcg/kg)[75]. Several randomized controlled clinical trials of ivermectin are underway (NCT04429711, NCT04530474, NCT04529525, NCT04602507). Currently, the National Institutes of Health recommend against the use of ivermectin for COVID-19 except in the clinical trials[9].

Summary guidance

The optimal treatment approach for COVID-19 is still not defined. We still have little data from large RCT which would guide the treatment of COVID-19. Findings from major studies on pharmacologic treatment of COVID-19 are summarized in Table 1 and recommendations are given in Table 2. The only large double-blind RCT reported so far showed only a modest benefit of the use of remdesivir[12] and the large Solidarity trial showed no survival benefit[14]. Based on the available evidence it seems prudent to give remdesivir to patients who need low-flow oxygen support. Although subgroup analyses should be interpreted with caution, in the Solidarity trial those with respiratory support but not on mechanical ventilation had a somewhat lower risk for death (Rate Ratio 0.86, 95% CI 0.67 to 1.11)[14]. Also, a subgroup analysis of ACTT-1 in patients receiving low-flow oxygen suggested a mortality benefit in those receiving remdesivir (Rate

Ratio 0.30, 95% CI 0.11 to 0.81)[14]. Currently, remdesivir has been recommended for the treatment of hospitalized patients with severe COVID-19[9,10] (Table 2). We should be reminded that fully powered blinded RCTs are considered the gold standard for clinical trials that produce high quality evidence of treatment effect. Until such trials are reported we should aim not to harm our patients. Currently, because of safety concerns and lack of proven benefit, chloroquine and hydroxychloroquine should not be used outside a closely monitored RCT. Other antiviral and immune-based therapy, including combination therapy should also be given through RCT. Although data on effectiveness of convalescent plasma and monoclonal antibodies targeting the receptor binding domain of the spike protein are emerging, those treatments should not be given routinely, and if given they should be administrated early, preferably within the first few days of symptomatic COVID-19[48-51].

The only recommendation that can currently be given is the use of corticosteroids, of which the most robust data comes from the Recovery trial which used dexamethasone 6 mg per day for up to 10 days[63]. The greatest benefit was observed among patients receiving mechanical ventilation. Of note, there was no benefit and even possible harm when dexamethasone was given to those who did not require oxygen supplementation at randomization.

Table 1. Overview of major randomized trials* on antiviral therapy for COVID-19 published till December 2020.
Tablica 1. Pregled značajnijih randomiziranih studija* o antivirusnom liječenju COVID-19 objavljenih do prosinca 2020.

Author/Study	Number of patients studied/analyzed (N)	Type of study	Conclusion	Comment
Beigel JH et al. Remdesivir for the treatment of Covid-19 – final report. N Engl J Med, 2020 ; 383:1813-1826. doi: 10.1056/NEJMoa2007764	Remdesivir iv (N=541) Placebo (N=521)	Double-blind, randomized, placebo-controlled trial	Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection.	Mortality still high in the remdesivir group. The primary outcome changed during the trial.
Goldman JD et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med, 2020; 383:1827-1837. doi: 10.1056/NEJMoa2015301.	Remdesivir iv for 5 days (N=200) Remdesivir iv for 10 days (N=197)	Randomized, open-label, phase 3 trial	No difference in efficacy between a 5 day and a 10 day course of remdesivir. 10 day course may be of benefit for patients who progressed to mechanical ventilation.	Lack of a randomized placebo control group. Only 44% of patients in the 10-day arm completed the full treatment course.
Wang Y et al., Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet, 2020; 395: 1569-78.	Remdesivir iv (N=158) Placebo (N=78)	Double-blind, randomized, placebo-controlled trial	Remdesivir use was not associated with a difference in time to clinical improvement and mortality at day 28, but patients with symptom duration of 10 days or less had faster time to clinical improvement.	Late initiation of treatment, more patients with hypertension, diabetes, or coronary artery disease in the remdesivir group.
Spinner CD, at al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA, 2020 ; Sep 15;324:1048-1057. doi: 10.1001/jama.2020.16349.	Remdesivir iv 10-days (N = 197) Remdesivir iv 5-days (N = 199) Standard care (N = 200)	Randomized open label trial	At day 11 patients randomized to a 5-day course of remdesivir had a better clinical status compared with standard care, but patients randomized to a 10-day course did not.	The clinical significance of the findings are unclear.
Kalil AC. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med, 2020 ; doi: 10.1056/NEJMoa2031994.	Remdesivir plus baricitinib (N=515) Remdesivir plus placebo (N=518)	Double-blind, randomized, placebo-controlled trial	Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or noninvasive ventilation.	No significant difference in mortality; the 28-day mortality was 5.1% in the combination group and 7.8% in the control group. Baricitinib was given without corticosteroids.

WHO Solidarity Trial Consortium. Repurposed Antiviral Drugs for Covid-19 —Interim WHO Solidarity Trial Results. N Engl J Med, 2020; doi: 10.1056/NEJMoa2023184.	N=11,330 adults Remdesivir N=2750 Hydroxychloroquine N=954 Lopinavir (without interferon) N=1411 Interferon N=2063 (including 651 to interferon plus lopinavir) No trial drug N=4088	Randomized open label trial	Remdesivir, hydroxychloroquine, lopinavir, and interferon had little or no effect on overall mortality, initiation of ventilation, and duration of hospital stay.	No placebo group.
Horby P, et al. Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med, 2020 ; 383: 2030-40.	Hydroxychloroquine. (N=1561) Usual care (N= 3155)	Randomized open label trial	Those who received hydroxychloroquine did not have a lower incidence of death at 28 days than those who received usual care.	Patients receiving hydroxychloroquine while not on invasive mechanical ventilation at the time of randomization were more likely to subsequently require intubation or die during hospitalization than those who received the standard of care.
Cavalcanti AB et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med, 2020 ;383:2041-2052. doi: 10.1056/NEJMoa2019014.	Hydroxychloroquine plus azithromycin (N=217) Hydroxychloroquine (N=221) Standard of care N= 229)	Randomized open label trial	Among patients hospitalized with mild- to-moderate Covid-19, the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status at 15 days as compared with standard care.	More adverse events occurred among patients who received hydroxychloroquine or hydroxychloroquine plus azithromycin than among those who received the standard of care.
Furtado RHM et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet, 2020; 396:959-967.	Azithromycin (N=214) Control group (N=183)	Randomized open label trial	In patients with severe COVID-19, adding azithromycin to standard of care did not improve clinical outcomes.	All patient in the standard group received hydroxychloroquine.
RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet, 2020 ; 396:1345-1352. doi: 10.1016/S0140-6736(20)32013-4.	Lopinavir/ritonavir (N=1616) Usual care (N=3424)	Randomized open label trial	Lopinavir-ritonavir was not associated with reductions in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death.	No placebo group.
Cao B, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med, 2020 ; DOI: 10.1056/NEJMoa2001282	Lopinavir-ritonavir (N=99) Standard care (N=100)	Randomized, controlled, open-label trial	No significant benefit of lopinavir-ritonavir in the time to clinical improvement, mortality at 28 day and viral clearance.	Trial was not blinded, there was a possibility of higher viral replication in the lopinavir-ritonavir group due to higher pharynx viral loads.
Hung IF et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. The Lancet, 2020; https://doi.org/10.1016/S0140-6736(20)31042-4	Combination group: lopinavir-ritonavir, ribavirin, interferon beta-1b (N=86) Control group: lopinavir-ritonavir (N=41)	Multicentre, prospective, open-label, randomized, phase 2 trial	Early triple antiviral therapy was safe and superior to lopinavir–ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19.	Need confirmation from larger phase 3 studies.

Ahmed S. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis, 2020 ; Dec 2:S1201-9712(20)32506-6.	Ivermectin (N=24) Ivermectin + doxycycline (N=24) Placebo (N=24)	Randomized, double-blind, placebo-controlled trial	Virological clearance was earlier in the 5-day ivermectin treatment arm versus the placebo group but not in the ivermectin + doxycycline arm.	
Libster R. et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. N Engl J Med, 2021 ; doi: 10.1056/NEJMoa2033700.	Convalescent plasma (N=80) Placebo (N=80)	Randomized, double-blind, placebo-controlled trial of convalescent plasma with high IgG titers	Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of Covid-19.	
Simonovich VA et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. New Engl J Med, 2020 ; doi: 10.1056/NEJMoa2031304.	Convalescent plasma (N=228) Placebo (N=105)	Double-blind, placebo-controlled, multicenter trial	No significant differences were observed in clinical status or overall mortality between groups.	
Li L et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. JAMA, 2020; 324:460-470. doi: 10.1001/jama.2020.10044.	Convalescent plasma in addition to standard treatment (N=52) Standard treatment alone (control) (N= 51)	Multicenter, prospective, open-label trial	No improvement in clinical status during 28 days of follow-up among patients receiving convalescent plasma compared to standard care in patients with severe or life-threatening COVID-19.	The trial was terminated early because of the waning epidemic and difficulties in recruiting new patients.
Agarwal A et el. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ, 2020 ; 371:m3939 http://dx.doi.org/10.1136/bmj.m3939	Convalescent plasma in addition to best standard treatment (N=235) Best standard treatment alone (control) (N=229)	Multicenter, prospective, open-label trial	Convalescent plasma was not associated with a reduction in progression to severe covid-19 or all cause mortality.	
Chen P et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med, 2020 ; doi: 10.1056/NEJMoa2029849. Online ahead of print.	Outpatients with recently diagnosed mild or moderate Covid-19 A single intravenous infusion of neutralizing antibody LY-CoV555 in one of three doses (700 mg, 2800 mg, or 7000 mg), N=309 Placebo, N=143	Phase 2 randomized double-blind placebo- controlled trial	Patients who received the 2800-mg dose of LY-CoV555 had a faster decline in viral load over time.	Results need confirmation from a larger trial. There were few events such as hospitalizations or emergency department visits. LY-CoV555 is also known as bamlanivimab.
ACTIV-3/TICO LY-CoV555 Study Group. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. N Engl J Med, 2020 ; doi: 10.1056/NEJMoa2033130.	All patients received best standard of care. LY-CoV555 (N=163) Placebo (N=151)	Randomized double-blind placebo- controlled trial	Among adult hospitalized patients who had a duration of symptoms of 12 days or less LY-CoV555, when coadministered with remdesivir, did not demonstrate efficacy	The data and safety monitoring board recommended stopping enrollment for futility.
Weinreich DM. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med, 2020 ; doi: 10.1056/NEJMoa2035002.	High-dose REGN-COV2, (N=90) Low-dose REGN-COV2 (N=92) Placebo (N=93)	Ongoing, double-blind, phase 1–3 trial involving nonhospitalized patients	The REGN-COV2 antibody cocktail reduced SARS-Cov-2 viral load. Effect was greater in patients whose immune response had not yet been initiated or who had a high viral load at baseline.	An interim analysis mainly on virological data. Clinical data evolving. REGN-COV2 is also known as casirivimab/imdevimab.

*Peer reviewed randomized trials only.

Table 2. Overview of World Health Organization (WHO), National Institutes of Health (NIH) and Infectious Diseases Society of America (IDSA) on treatment of COVID-19 as of December 2020.

Tablica 2. Pregled preporuka Svjetske zdravstvene organizacije (SZO), National Institutes of Health (NIH) i Infectious Diseases Society of America (IDSA) o liječenju COVID-19, prosinac 2020.

Drugs	WHO	NIH	IDSA
Remdesivir	Recommendation against use (weak or conditional recommendation)	Mild, moderate and hospitalized not requiring oxygen: insufficient data Hospitalized and requires supplemental oxygen[a]: recommended Hospitalized and requires supplemental oxygen with a high flow device or noninvasive ventilation: recommended[b] Hospitalized and on invasive mechanical ventilation or ECMO: not recommended.	Mild, moderate and hospitalized not requiring oxygen: suggest against routine use Severe[c] disease, hospitalized and requires supplemental oxygen: suggested
Hydroxychloroquine (HCQ), Chloroquine, HCQ with Azithromycin, Lopinavir/ ritonavir,	Strong recommendation against use	Recommendation against use	Recommendation against use
Corticosteroids for patients with non-severe COVID-19	Recommendation against use (weak or conditional recomendation)	Dexamethasone should not be used[d]	Suggest against use
Corticosteroids for patients with severe and critical COVID-19	Systemic corticosteroids recommended	Dexamethasone recommended	Suggested[e] or recommended[f]
anti-IL-6 receptor monoclonal antibodies	Not mentioned	Recommends against the use of anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) or anti-IL-6 monoclonal antibody (siltuximab), except in a clinical trial	Suggested against routine use
convalescent plasma bamlanivimab, casirivimab plus imdevimab		There are insufficient data for to recommend either for or against	Recommended only in clinical trials (bamlanivimab) Suggested against routine use (plasma)

[a] Recommended only with dexamethasone (moderate recommendation, expert opinion).

[b] In nonhospitalized patients, the Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19, except in a clinical trial.

[c] Severe illness is defined as patients with SpO2 ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO. In patients on supplemental oxygen but not on mechanical ventilation or ECMO, the panel suggests treatment with five days of remdesivir rather than 10 days of remdesivir.

[d] Not hospitalized, mild to moderate disease

[e] Among hospitalized patients with severe, but non-critical, COVID-19 the panel suggests dexamethasone.

[f] Among hospitalized critically (on mechanical ventilation or extracorporeal membrane oxygenation or end organ dysfunction as is seen in sepsis/septic shock) ill patients with COVID-19, the panel recommends dexamethasone.

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