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Host-modifying drugs against COVID-19: some successes, but not yet the breakthrough

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Summary

After reviewing antiviral drugs (Brüssow Environmental Microbiology 2021) the present review summarizes the results of clinical trials with host-modifying drugs in COVID-19 patients. Clinical benefits were observed with different immunomodulators. The variable outcomes of trials with the interleukin 6 receptor inhibitor tocilizumab demonstrated that treatment benefits might only be present in specific subgroups of patients or in specific infection stages. A meta-analysis of trials with the interleukin 1 receptor antagonist anakinra showed a survival benefit only in patients with hyperinflammation. The Janus kinase inhibitor baricitinib is an anti-inflammatory treatment that showed a clinical benefit in hospitalized patients who do not yet need supplementary oxygen. In contrast, the corticosteroid dexamethasone showed mortality reducing effects that were limited to patients on ventilation or in need of supplementary oxygen. Therapeutic dose of anticoagulation met the criteria for inferiority in severe cases, but showed a small survival benefit in non-severe COVID-19 patients. Large trials with colchicine showed a small or no survival benefit. Azithromycin, an antibiotic with immunomodulatory activity, showed no effects in numerous clinical trials. The trials showed a clear need for new drugs instead of repurposed drugs and drugs that specifically target the SARS-CoV-2 virus or the pathology developing in COVID-19 patients.

Introduction

Drug development against COVID-19 was led by concepts of the emerging pathophysiology for this new disease (Osuchowski *et al*., 2021). Most models consider two pathways of damage that lead to the observed clinical signs. In the early infection phase, the pathology is determined by the direct cell damage of the viral infection. By its receptor specificity, SARS-CoV-2 targets primarily epithelia of the upper and then the lower respiratory tract, but also actively replicates on intestinal epithelia and can infect endothelial cells and heart cells. The infection initiates in ciliated cells of the nasal cavity from where the infection can disseminate either by viremia or by aspiration into the lung where the major pathology occurs. It was thus logical that one major activity of COVID-19 drug development looked for antiviral agents, the subject of a recent minireview (Brüssow, 2021). However, pathophysiological research identified impaired gas exchange in the lungs induced by oedema, congestion, fibrotic processes and coagulopathies as basis for clinical symptoms observed in more severe infections. Endothelial damage and the increased release of pro-inflammatory cytokines and chemokines subsequently took centre stage for the understanding of the pathology of severe COVID-19 where a 'cytokine storm' causes a systemic inflammatory response responsible for multiorgan damage. A maladaptive, dysregulated immune response further complicates COVID-19, where the immune response to the viral infection becomes a driver of pathology in severe COVID-19. Based on these concepts, a second approach to COVID-19 drug development targeted host reactions, the focus of this minireview. Since cytokines played a central role in these concepts, inhibitors of interleukins, e.g. IL-6, and interleukin receptors, e.g. IL-1R, or drugs interfering with the intracellular signalling pathway of cytokines, e.g. Janus kinase (JAK) inhibitors or drugs stimulating the sigma-1 receptor (S1R), received much attention. Drugs that dampen inflammatory responses such as corticosteroids or agents which interfere with inflammatory pathway signalling such as the granulocyte–macrophage colony-stimulating factor

(GM-CSF) receptor were a further focus of COVID-19 drug research. Other clinicians explored anticoagulation strategies since pathologists had reported widespread arterial and venous thromboembolism in COVID-19 patients. The current overview summarizes the outcome of clinical trials with these host-modifying drugs in COVID-19 patients. This overview also covers immuno-modulatory compounds such as the antibiotic azithromycin (AZ), the antineoplastic drug imatinib, the anti-rheumatic drug colchicine or the effect of organ-protective drugs such as glifozins.

Clinical trial overview: immunomodulators

IL-6 receptor inhibitor: tocilizumab

Exploratory studies. Greek researchers observed low expression of the human leukocyte antigen (HLA)-DR on CD14 monocytes in COVID-19 patients in need of mechanical ventilation. These patients showed a unique combination of defective antigen presentation and lymphopenia. Interleukin-6 (IL-6) and C-reactive protein (CRP) were significantly increased in these severe cases. IL-6 is known to inhibit HLA-DR expression. The authors suggested clinical trials to explore a specific blocker of the IL-6 pathway such as tocilizumab (Giamarellos-Bourboulis *et al*., 2020).

Chinese scientists investigated 48 COVID-19 patients with different disease severity and identified viral RNA in the blood and high IL-6 levels as biomarkers of severe disease (Chen *et al*., 2020). Tocilizumab is a recombinant humanized monoclonal antibody that binds the IL-6 receptor and inhibits signal transduction. Clinically it is used for the treatment of some forms of juvenile arthritis. In a small exploratory trial with tocilizumab in 21 patients suffering from severe COVID-19 fever disappeared in all patients, CRP – an infection marker – returned to normal in most of them, peripheral oxygen saturation improved, radiologic lung damage ameliorated and the virus load was cleared (Xu *et al*., 2020).

Italian trial. Subsequently, 1351 Italian patients admitted with severe COVID-19 pneumonia were attributed to either tocilizumab or standard therapy alone. Tocilizumab led to a significant reduction of the composite primary endpoint: invasive mechanical ventilation (IMV) or death compared to standard therapy (23% vs. 37%). The effect on mortality was even greater (7% vs. 20%). A comparable effect was seen for intravenous and subcutaneous application of tocilizumab. The patients differed at baseline for comorbidities and cough (both greater in the treatment group) and the treatment and control groups differed for concomitant glucocorticoid treatment (30% vs. 17%) raising the question of treatment interactions.

There was no difference for secondary infections, the major concern with immunomodulatory treatment, between treatment and controls groups (Guaraldi *et al*., 2020).

US trials. In an observational study from the United States, tocilizumab or placebo was given to 154 COVID-19 patients requiring mechanical ventilation. After a month, 18% of treated and 36% of control patients had died. Treated patients also showed an improved status on the ordinal outcome scale compared to controls. However, tocilizumab was also associated with an increased proportion of patients with superinfections (54% vs. 26%), mostly with *Staphylococcus aureus* (Somers *et al*., 2021).

A retrospective observational cohort study was conducted in New Jersey/US with 210 COVID-19 patients who received tocilizumab and 420 who served as controls. Mortality was 49% and 61%, respectively. In a multivariable regression analysis, a significant association was noted between receiving tocilizumab and decreased hospital-related mortality, but the beneficial effect was only seen in patients with CRP (an inflammation marker) greater than 15 mg dl^{-1} at baseline. Tocilizumab also induced a reduction in CRP levels. Treatment was not associated with an increase in secondary bacteremia and steroid use was not associated with improvement in survival (Biran *et al*., 2020).

Physicians from Boston conducted a randomized, double-blind, placebo-controlled trial with tocilizumab in 243 COVID-19 patients displaying a hyperinflammatory state and in need of supplemental oxygen. The primary outcome was intubation or death, the secondary efficacy outcomes were clinical worsening or discontinuation of supplemental oxygen. For none of these parameters a significant difference was detected between the two groups. Neutropenia developed in significantly more patients in the treatment than in the placebo group, but despite that fewer patients on tocilizumab than placebo developed serious superinfections (Stone *et al*., 2020).

UK trial REMAP-CAP. This trial explored the effect of tocilizumab given to 353 COVID-19 patients within 24 h after starting organ support in the intensive care unit (ICU) compared to 402 control patients. The trial accounted for potential treatment-by-treatment interactions since glucocorticoids were given to >80% of the patients. The median number of organ support–free days was 10 days in the tocilizumab and 0 days in the control group. The in-hospital mortality in treated patients was 27% compared to 36% in the control group. The effect of the tocilizumab/glucocorticoids combination was greater than for each intervention on its own (REMAp-CAP Investigators, 2021a).

COVACTA. The COVACTA trial conducted in eight European countries and the United States randomized 294 patients with severe COVID-19 pneumonia to tocilizumab and 144 patients to placebo. The primary outcome was clinical status at day 28 on an ordinal scale which was marginally better in the treatment group. Mortality at day 28 was 19.7% in the tocilizumab and 19.4% in the placebo group. The median time until patients were discharged from the hospital was 20 and 28 days, respectively, and the median duration of ICU stay was 9.8 days in the tocilizumab and 15.5 days in controls. The initiation of mechanical ventilation was 28% and 37% and transfer to the ICU occurred in 21% and 36% in the treatment and the control group, respectively. However, none of these trends was statistically significant. Adverse events were not associated with the treatment (Rosas *et al*., 2021).

EMPACTA. The EMPACTA study investigated the effect of tocilizumab in minority populations from the United States (Hispanic, Black, American Indian). A total of 389 patients hospitalized with COVID-19 pneumonia were randomized on a 2:1 basis on tocilizumab or placebo, both groups received standard therapy which included glucocorticoids for 78% of the patients and antivirals in 60% of the patients. The primary outcome was mechanical ventilation or death by day 28 which occurred in 12% and 19.3% of the treatment and control group, respectively, representing a significantly lower percentage of disease progression. However, the death rate was similar in both groups: 10.4% versus 8.6%. Median time to hospital discharge was 1.5 days shorter in the treatment group (Salama *et al*., 2021).

Various international trials. Tocilizumab was given to 90 patients hospitalized with moderate to severe COVID-19 in India and compared to 90 patients receiving only standard care. Overall, no significant amelioration in disease outcome was seen. However, *post hoc* evidence from this study suggests tocilizumab to be effective in patients with severe COVID-19 (Soin *et al*., 2021). In a trial conducted in 11 countries, 431 COVID-19 patients with oxygen supplementation or intensive care were randomized on placebo or two different doses of intravenous sarilumab, another IL-6 receptor inhibitor. The primary endpoint was time to clinical improvement and the secondary endpoint was the proportion of patients alive at day 29. No significant differences between the treatment groups were seen for the primary or the secondary outcome (Lescure *et al*., 2021).

The French CORIMUNO trial enrolled 131 COVID-19 pneumonia patients requiring oxygen supply but no ventilation. The interim report showed less need of subsequent ventilation in the treatment group (24% vs. 36% in usual care), but day 28 mortality did not differ between the two groups (Hermine *et al*., 2021). In another small Italian study, 126 COVID-19 patients were treated with tocilizumab early after hospitalization or with standard care. 28% and 27% of the patients in the two groups showed clinical worsening and a similar rate of intubation or death in both groups (Salvarani *et al*., 2021).

UK RECOVERY trial. A clear answer on the use of tocilizumab was provided by a large RECOVERY trial where 2022 hospitalized COVID-19 patients were randomly allocated to tocilizumab and 2094 to usual care. Mean age of the patients was 64 years and 41% were receiving non-invasive respiratory support and 14% needed IMV. The researchers observed a significant reduction in the primary outcome of 28-day mortality (31% vs. 35%), a greater probability of discharge from hospital within 28 days (57% vs. 50%), and a reduction in the risk of progressing to IMV or death (35% vs. 42%). All differences were statistically significant. The authors of this study conducted a meta-analysis of all eight studies published with tocilizumab treatment and observed a 14% proportional reduction in 28-day mortality. They noted an additive effect when tocilizumab is combined with corticosteroids resulting in mortality reduction by a third up to a half according to the severity of oxygen support. Since no more bacterial infections were observed under tocilizumab treatment than in controls, the authors of the RECOVERY study requested an update of clinical guidelines and proposed to include tocilizumab for the treatment of COVID-19 (Recovery Collaborative Group, 2021b).

Interpretation of different outcomes. The variable outcomes of the tocilizumab trials highlight problems with small clinical trials that provide equivocal results because treatment benefits might only be present in specific subgroups of patients or in specific infection stages. Small trials do not allow meaningful planned subgroup analyses. The authors of the French CORIMUNO trial asked what might explain the heterogeneity in the outcome of the different tocilizumab trials. Extending their trial evaluation to 90-day survival still did not allow them to observe a significant difference between the tocilizumab and the control group. They reasoned that improved 28-day survival was demonstrated only in the two largest studies and those with the highest mortality, RECOVERY and REMAP-CAP. Moreover, only RECOVERY enrolled patients with elevated CRP levels. Indeed, when they stratified the patients from the CORIMUNDO trial for the CRP level, the high CRP subgroup treated with tocilizumab showed a significantly lower 90-day mortality compared to the control group (Salvarani *et al*., 2021).

IL-1 receptor antagonist: Anakinra

In some patients, SARS-CoV-2 induces a hyper-inflammatory syndrome in which the interleukin (IL)-1/IL-6 pathway is involved. Anakinra, a recombinant IL-1 receptor antagonist, was thus a logical choice for drug trials.

French trials. A small French trial in 12 anakinra-treated patients showed a rapid decrease of temperature and inflammation marker and development of oxygen independence compared to 10 controls. While four controls needed invasive ventilation, this was only the case in two anakinra-treated patients (Cauchois *et al.*, 2020).

In another French study, 52 COVID-19 patients with bilateral pneumonia and radiologically confirmed lung infiltration were treated with subcutaneous anakinra and compared with 44 historical controls from the same hospital. The main outcome was a composite of either admission to the ICU for IMV or death which occurred in 25% of the treated patients and in 73% of the historical controls. Treatment with anakinra also reduced the mortality and induced a decrease of CRP levels compared to controls (Huet *et al.*, 2020).

Italian trials. During the particularly severe first infection wave in Northern Italy hospitals were overburdened and had not enough ICU beds for COVID-19 patients with hyperinflammation. Clinicians from a hospital in Milan treated 29 patients with high-dose intravenous anakinra and non-invasive ventilation; 16 patients on standard treatment served as controls. At 21 days, anakinra treatment was associated with reductions in serum CRP and progressive improvements in respiratory function and only 10% died compared to 44% among the controls (Cavalli *et al.*, 2020). Subsequently, the clinicians from Milan compared two IL inhibitors in COVID-19 patients with respiratory insufficiency and hyperinflammation. The patients received either the IL-1 receptor inhibitor anakinra ($n = 62$), an IL-6 receptor inhibitor ($n = 55$) or no inhibitors ($n = 275$). The 28-day survival rate was 68% in patients who did not receive an inhibitor, 86% in patients treated with IL-1 receptor inhibitor, and 82% in patients treated with IL-6 receptor inhibitor. In a multivariate analysis considering baseline criteria, only the IL-1 receptor inhibitor had a significant effect on mortality reduction. Subgroup analysis showed that IL-6 receptor inhibition might be advantageous for patients with very high serum concentrations of CRP. The benefit of both IL-1 and IL-6 inhibition was more pronounced in patients in an early disease state (Cavalli *et al.*, 2021).

Another group of clinicians from Milan explored a combination of anakinra with methylprednisolone (MP) (a glucocorticoid) in 65 severe COVID-19 patients with pneumonia and hyperinflammation, compared to 55 untreated historical controls. At 28 days, mortality was 14% in treated patients and 36% in controls and the treatment was associated with consistent improvements in respiratory function and a rapid lowering of serum CRP level (Bozzi *et al.*, 2021). Another study compared the effect of anakinra alone ($n = 30$) or in combination with MP ($n = 33$) compared to standard of care in 65 control COVID-19 patients. In this retrospective study, anakinra with or without MP reduced the mortality by 70% when given early (Pontali *et al.*, 2021).

Greek trial. A multicentre trial from Greece compared the outcome in 130 COVID-19 patients showing a biochemical marker heralding a risk of progression to severe respiratory failure (SRF). Patients were treated with subcutaneous anakinra and compared to 130 score-matched controls receiving only standard of care. 22% of the anakinra-treated patients progressed to SRF compared to 59% in controls; 30-day mortality was 12% and 22%, respectively. Direct comparisons were complicated by baseline differences between the two groups. Anakinra treatment increased the lymphocyte count, decreased the IL-6 concentration and cut the hospitalization cost by a factor of 2 (Kyriazopoulou *et al.*, 2021a).

CORIMUNDO controlled trial. Only a single multicentre, open-label, randomized clinical trial was conducted with anakinra. In the French CORIMUNDO-ANA-1 trial 59 patients with mild-to-moderate COVID-19 received injected anakinra versus 57 receiving usual care. The trial was stopped at interim analysis for futility. On day 4 of treatment, the clinical score did not differ from controls; on day 14, 47% of treated and 51% of the control patients needed mechanical ventilation or died. On day 90, survival was identical in both groups (72%). No effect of anakinra on CRP inflammation marker or on lymphocyte counts compared to controls was seen (CORIMONDO collaborative group, 2021).

Meta-analysis. Aggregate data from nine studies, comprising 1185 patients (509 on anakinra and 676 controls), showed a significant reduction in mortality in anakinra-treated patients. In an individual patient-level meta-analysis comprising 895 patients, 11% of 342 anakinra-treated and 25% of 553 patients receiving standard of care died. The survival benefit was most profound in patients with hyperinflammation probably explaining the lack of an effect in the only controlled trial since it had a low cut-off for CRP levels as an inclusion criterion into the trial. The authors of the meta-analysis did not observe a significant survival benefit of anakinra when co-administered with dexamethasone. Anakinra needs to be given early, as application in patients on mechanical ventilation was not efficient (Kyriazopoulou *et al.*, 2021b).

JAK inhibitors: baricitinib

JAK inhibitor. Baricitinib is an oral, selective inhibitor of Janus kinases JAK 1 and 2 with potent anti-inflammatory activity, and clinically approved for the treatment of rheumatoid arthritis. JAK is a family of intracellular, non-receptor tyrosine kinases that transduce cytokine-mediated signals via the JAK–STAT pathway. Baricitinib inhibits the intracellular signalling pathway of cytokines, including IL-2, IL-6, IL-10 and interferon-γ. Therefore, the use of therapeutics targeted at JAKs has the potential to reduce disease severity by limiting the cytokine release syndrome.

Preclinical study. US virologists studied the effect of baricitinib in rhesus monkeys challenged with SARS-CoV-2. After SARS-Cov-2 infection, control monkeys showed an accumulation of inflammatory macrophages and neutrophils in the lungs. Baricitinib treatment reduced the levels of macrophages producing inflammatory cytokines and neutrophil-attracting chemokines, decreased the infiltration of neutrophils into the lung and reduced T cell activation, but baricitinib had no inhibitory activity on viral replication; nevertheless, lung pathology in the monkeys was mild (Hoang *et al*., 2021).

Small trials. A small Chinese trial which randomized 43 severe COVID-19 patients on the JAK inhibitor ruxolitinib or placebo in addition to standard therapy which included corticosteroids (70%) and antivirals (90%) showed a faster improvement in chest tomography, less mortality (0 vs. 3 deaths), faster recovery from lymphopenia and a marked decrease in cytokines in the treatment compared to the control group (Cao *et al*., 2020). A small uncontrolled cohort of 15 US COVID-19 patients with moderate-to-severe disease received the JAK inhibitor baricitinib; 13 patients experienced a significant body temperature and CRP levels decrease and 12 patients had a clinical improvement with respect to oxygen requirement, but three patients died (Titanji *et al*., 2021). In an Italian and a Spanish hospital 600 COVID-19 patients with moderate-to-severe pneumonia were enrolled into a study; 83 patients were treated with baricitinib and matched to an equal number of patients not treated with this JAK inhibitor. In the merged matched population, the primary composite endpoint of death or IMV occurred in 17% of baricitinib-treated and 35% of control patients. Baricitinib's favourable effect appeared 'early' upon treatment and was maintained despite some attrition (Stebbing *et al*., 2021).

ACTT-2 trial. NIH clinicians asked whether a combination of an antiviral with an agent reducing inflammation would have a better effect than an antiviral alone. To answer this question a total of 1033 patients underwent randomization in the ACTT-2 trial. All patients received remdesivir (≤10 days) and either baricitinib (≤14 days) or placebo (control). Patients on the combined treatment had a median time to recovery of 7 days compared to 8 days in remdesivir alone recipients. The difference was small but significant. No difference was seen for patients with moderate disease at baseline, while patients receiving high-flow oxygen or noninvasive ventilation at enrolment had a time to recovery of 10 days with combination treatment and 18 days without. Baricitinib/remdesivir-treated patients showed a better improvement in clinical status at day 15 than those receiving only remdesivir, but the 28-day mortality did not differ significantly (5.1% vs. 7.8%) (Kalil *et al*., 2021).

Brazilian trial. A total of 289 COVID-19 patients with pneumonia, but not receiving ventilation, were randomized on the JAK inhibitor tofacitinib or placebo (89% of all patients also received glucocorticoids). The primary outcome of death or respiratory failure through day 28 was significantly lower in the treatment compared to the control group (18% vs. 29%). Death rates were non-significantly reduced: 2.8% versus 5.5% (Guimarães *et al*., 2021).

COV-barrier trial. A total of 1525 COVID-19 patients from 12 countries were randomized on a 1:1 basis on oral baricitinib or placebo. At baseline, 79% received systemic corticosteroids. The composite primary endpoint was the proportion who progressed to high-flow oxygen, non-invasive ventilation, IMV, or death by day 28, which did not differ between the groups (27.8% in the treatment and 30.5% in the control group for the composite endpoint). However, the 28-day all-cause mortality was with 8% for the baricitinib and 13% for the placebo recipients significantly reduced in the baricitinib group, indicating a 38% relative reduction in mortality which translates into one additional death prevented per 20 baricitinib-treated patients. An even greater mortality reduction from 15% in controls to 5% in the treatment group was seen in the subpopulation of patients on supplementary oxygen (SO) at baseline (Marconi *et al*., 2021).

Evaluation. According to a NEJM editorial, JAK inhibitors have two interesting aspects. Anti-inflammatory treatment with glucocorticoids and the JAK inhibitor, which acts in a mechanistically different way, provides additive benefits. In addition, glucocorticoids or glucocorticoids combined with IL-6 receptor antagonists are indicated for patients who are classified between 5 and 7 on the NIH ordinal clinical scale, while JAK inhibitors also displayed benefits in patients classified as 4 on the ordinal scale (hospitalized but not receiving SO), thus giving greater therapeutic flexibility to the clinician (Stebbing and Lauschke, 2021).

Fluvoxamine

Fluvoxamine stimulates the S1R which regulates cytokine production. Cytokine reduction leads to anti-inflammatory actions resulting from S1R activation. US physicians enrolled 80 confirmed COVID-19 outpatients suffering from fatigue or loss of smell to fluvoxamine and 72 matched outpatients to placebo. During follow-up, none of the subjects in the treatment group, but six of the placebo recipients showed deterioration of symptoms (four were hospitalized for COVID-19, one required mechanical ventilation). While encouraging, the physicians qualified their observations as an interesting working hypothesis rather than a demonstration of efficacy, because of the small patient number and the remote conduct of the trial (Lenze *et al*., 2020).

Corticosteroids

In severe viral pneumonia caused, e.g. by influenza or SARS, the host immune response contributes to organ failure. Therefore, decreasing the immune response might therefore also help in COVID-19. However, early guidelines from the WHO advised against the systematic use of glucocorticoids in COVID-19, for fear of suppressing antiviral immune responses (Russell *et al*., 2020).

Dexamethasone. Dexamethasone is a glucocorticoid used to treat rheumatic problems, severe allergies, asthma and a number of other diseases. The RECOVERY trial in the United Kingdom assigned 2104 hospitalized COVID-19 patients to oral or intravenous dexamethasone (6 mg once daily for 10 days) and 4321 patients to standard of care. The primary outcome was 28-day mortality. Overall, 22.9% in the dexamethasone group and 25.7% in the usual care group died within 28 days after randomization. The effect of dexamethasone differed substantially with the respiratory support needed by the patients at randomization. 16% of the patients in this study received IMV, 60% oxygen only, and 24% no respiratory support. In the ventilation group, death occurred in 29.3% of the treated and 41.4% of the control patients; in the oxygen requiring group the difference was less important, but still statistically significant (23.3% vs. 26.2%), while among those without respiratory support, more deaths were observed in the dexamethasone group than in the controls (17.8% vs. 14.0%), potentially indicating a treatment-induced harm (Recovery Collaborative Group, 2021). The dexamethasone RECOVERY trial was the first drug trial demonstrating a modest, but significant mortality reduction in defined subgroups of treated COVID-19 patients. Dexamethasone treatment became immediately part of the treatment guidelines in the United Kingdom and elsewhere. Numerous ongoing glucocorticoid trials stopped patient recruitment since it was considered unethical to randomize patients on glucocorticoids or placebo when the mortality reduction was demonstrated in a large trial.

Brazilian clinicians treated 299 COVID-19 patients in the CoDEX trial with moderate to severe acute respiratory distress syndrome (ARDS) with a daily dose of 20 mg intravenous dexamethasone or standard care. The dexamethasone group had a higher number of ventilator-free days than controls, but there was no significant difference between the groups for day 28 mortality, ICU-free days, or clinical scores on an ordinal scale. The clinicians attributed the different outcome compared to the RECOVERY trial to the higher mortality risk in the Brazilian patients (Tomazini *et al*., 2020).

Egyptian clinicians treated 109 critically ill COVID-19 patients with either tocilizumab or dexamethasone. Dexamethasone-treated patients showed a better recovery of respiratory function and a better survival (Rashad *et al*., 2021).

Methylprednisolone. Methylprednisolone (MP) is a synthetic glucocorticoid, primarily prescribed for its anti-inflammatory and immunosuppressive effects. Columbian clinicians compared the clinical outcome of 111 COVID-19 patients with pneumonia treated with the low dexamethasone dose used in the RECOVERY trial with that of 105 patients receiving a high dose of MP. 26% of the dexamethasone-treated, but only 17% of the MP-treated patients developed ARDS. Patients from the MP group experienced less transfer to an ICU (4.8% vs. 14.4%) and had a shorter recovery time than patients from the dexamethasone group and the 30-day survival was also significantly greater with 92.6% versus 63.1%. The clinicians suggested that the inferiority of dexamethasone compared to MP might be due to a too low dose of dexamethasone given or a consequence of the concomitant treatment of the Columbian patients with colchicine (Pinzón *et al*., 2021). Iranian clinicians also compared MP and dexamethasone treatment in 86 COVID-19 patients. After treatment, the MP recipients showed a lower clinical score on an ordinal scale, a trend for lower mortality, a shorter hospital stay and less ventilator need than the dexamethasone recipients (Ranjbar *et al*., 2021). A total of 416 COVID-19 patients from Manaus/Brazil in very critical conditions were randomized on MP or placebo. The primary endpoint, the mortality at day 28, was not different between the two groups and no difference in viral clearance was seen. A post hoc subgroup analysis showed a mortality reducing effect of MP only in patients older than 60 years. The clinicians suspected that a shorter course of treatment (5 days compared to 10 days in the RECOVERY trial) could

explain the lack of a beneficial effect (Prado Jeronimo *et al*., 2021).

In a small Spanish clinical trial 64 hospitalized COVID-19 patients receiving oxygen but no mechanical ventilation were randomized on intravenous MP or standard of care. The primary outcome (death, admission to the ICU, or requirement of noninvasive ventilation) did not differ in an intention-to-treat analysis, but a per-protocol analysis associated a significant benefit to the use of MP (Corral-Gudino *et al*., 2021).

Hydrocortisone. Hydrocortisone (HC) is the name for the hormone cortisol, a glucocorticoid secreted by the adrenal cortex, when supplied as a medication. HC is used to treat immune, inflammatory and neoplastic conditions. A total of 403 severe COVID-19 patients from the REMAP-CAP trial were randomized at transfer to ICU on a fixed dose of HC, received HC only when going into shock or received no HC. The in-hospital mortality was 30%, 26% and 33% respectively in the three groups. The trial was stopped early since no treatment strategy reached the predefined statistical superiority for clinical benefits (REMAP-CAP Investigators, 2020).

A French trial comparing HC with placebo was also stopped after the enrolment of 149 severe COVID-19 patients. Treatment failure, defined as death, persistent need of mechanical ventilation or need for high-flow oxygen, was not statistically different between the groups (42% vs. 51%). Mortality showed a non-significant trend towards lower values in the HC group, 15% vs. 27% (Dequin *et al*., 2020).

Meta-analyses: oral or injected corticoids. The WHO commissioned a meta-analysis of seven clinical trials for an association between systemic use of glucocorticoids and all-cause mortality at day 28 after randomization in 1703 critically ill COVID-19 patients. There were 222 deaths among the 678 patients treated with corticosteroids and 425 deaths among the 1025 control patients, a significant death reduction by one third. The reduction was significant for dexamethasone (three trials), but not for HC and MP (WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, 2020).

A more recent Cochrane meta-analysis included 11 randomized, controlled trials (RCTs) with 8075 enrolled participants; 3072 participants were randomized to the corticosteroid arms with the majority receiving dexamethasone ($n = 2322$). The authors noted further 42 ongoing trials with corticosteroids. Systemic glucocorticoids reduced all-cause mortality slightly (risk ratio 0.89), together with a slight reduction in ventilator-free days. The authors identified a need to identify the effective dose and the subgroup of patients who will

most profit from corticosteroid application (Wagner *et al*., 2021).

Inhaled glucocorticoids. Epidemiological observations showed that asthma patients were significantly underrepresented in COVID-19 patients admitted to the hospital. British researchers hypothesized that this might be due to the widespread use of inhaled glucocorticoids in these patients and randomized 146 outpatients within 7 days of the onset of mild COVID-19 symptoms on the glucocorticoid budesonide by inhalation (800 µg per actuation) or usual care. The primary endpoint was COVID-19-related urgent care visit, including emergency department assessment or hospitalization which occurred in 3% of the treatment and 15% of the control patients. Self-reported clinical recovery was 1 day quicker with budesonide than in the control group and the treated participants experienced less fever. Unfortunately, the trial was stopped early after an independent statistical review concluded that further patient recruitment would not change the conclusion. This important clinical observation is thus only based on observations from 73 treated participants (Ramakrishnan *et al*., 2021). In a PRINCIPLE trial with 2530 SARS-CoV-2-positive older British outpatients, where 787 were treated with budesonide, 1069 with usual care, and 974 with other treatments, inhaled budesonide improved time to recovery, with a chance of also reducing hospital admissions or deaths, but the results did not meet the predefined superiority threshold (Yu et al., 2021).

Colchicine

Colchicine, an inhibitor of tubulin polymerization, is an old plant-derived drug. Due to its effect on the inflammasome, it has a potent anti-inflammatory action that is clinically used for the treatment of gout, joint swelling and viral pericarditis. Colchicine is safe, cheap, widely available and can be administered orally. Greek physicians randomized 105 COVID-19 patients on colchicine or standard treatment in a prospective, open-label randomized trial. The colchicine group experienced less clinical deterioration (mechanical ventilation or death) than the control (2% vs. 14%). The results, albeit significant, should be interpreted with caution because of the small number of enrolled patients due to the declining epidemic in Greece. The observation of anti-thrombotic and anti-inflammatory activities of colchicine by clinical chemistry observations warrants confirmation in larger clinical trials (Deftereos *et al*., 2020; Rabbani *et al*., 2020).

A total of 4488 COVID-19 outpatients from three continents with at least one high-risk factor for severe disease development (mostly high BMI or diabetes) were randomized on oral colchicine or placebo. The primary efficacy

endpoint was the composite of death or hospital admission for COVID-19 within 30 days. For all enrolled patients, the rates were 4.7% versus 5.8%, the difference was only statistically significant when restricted to patients with a PCR-confirmed COVID-19 diagnosis (4.6% vs. 6%). Colchicine was associated with a higher rate of adverse reactions, mostly diarrhoea. Due to the small effect size, reproduction of the results by another trial was recommended by the authors (Tardif *et al*., 2021).

In a RECOVERY trial, 5610 hospitalized COVID-19 patients from the United Kingdom were randomized on oral colchicine and 5730 on a placebo plus usual care (94% of all patients were treated with a glucocorticoid). The primary outcome was 28-day mortality, which was 21% in both groups and consistent among all pre-specified patient subgroups (including those not treated with glucocorticoids). No difference was seen between the two groups for secondary outcomes such as duration of hospitalization (10 days), discharge alive from the hospital within a month (70%) or progression to IMV (25%) (Recovery Collaborative Group, 2021).

GM-CSF receptor inhibitor: Mavrilimumab

GM-CSF is a cytokine involved in inflammation. Its binding to the GM-CSF receptor-α (GM-CSFRα) activates multiple pro-inflammatory pathways. In macrophages and neutrophils, GM-CSFRα activation causes secretion of tumour necrosis factor and of various ILs including IL-6. GM-CSF thus functions as a feedforward inflammatory amplifier potentially involved in the cytokine storm described in severe COVID-19. The pathogenesis of COVID-19 pneumonia involves a maladaptive, detrimental inflammatory response in the lungs. Mavrilimumab is a monoclonal antibody (mab) that binds to the GM-CSFRα receptor and disrupts its downstream signalling. Mavrilimumab has shown efficacy in patients with rheumatoid arthritis.

Italian clinicians compared the outcome in 13 severe COVID-19 pneumonia patients with systemic hyper-inflammation treated with intravenous mavrilimumab and in 26 matched control patients receiving standard care. On day 28, all treated patients showed clinical improvement compared with 65% of the controls. 8% of the treated and 35% of the control patients progressed to mechanical ventilation; none of the treated, but 27% of the controls died, but due to the small number of patients none of the differences was statistically significant (De Luca *et al*., 2020).

In a small US trial, 40 COVID-19 patients hospitalized with pneumonia were randomized on intravenous mavrilimumab or placebo. On day 14, 57% of patients in the mavrilimumab group were alive and off supplemental oxygen therapy compared with 47% of patients in the placebo group. On day 60, mortality in the treatment group was 5% compared with 21% in the placebo group. Again, none of these differences was statistically significant (Cremer *et al*., 2021).

Azithromycin

AZ is a macrolide antibiotic used against bacterial infections of the lower respiratory tract with activity against Gram-positive bacteria and atypical pathogens. AZ is also used to treat chronic inflammatory lung disease since it has immunomodulatory activity by decreasing the production of pro-inflammatory cytokines and inhibiting neutrophil activation. AZ was shown to decrease mortality from pneumonia caused by influenza. Immunomodulatory activity has been attributed to AZ based on in vitro, animal and observational data. According to a survey of more than 6000 physicians in 30 countries, AZ was the second most commonly prescribed treatment for COVID-19 after hydroxychloroquine (HCQ) in the early phase of the pandemic. Political support for HCQ and AZ was particularly high in Brazil.

COALITION I and II trials. Brazilian clinicians conducted a multicentre, randomized, open-label, controlled trial (COALITION I trial) involving 504 patients, hospitalized with mild-to-moderate molecularly confirmed COVID-19. The patients were randomly assigned to receive standard care, standard care plus HCQ, or standard care plus HCQ plus AZ. The primary outcome was clinical status at 15 days as assessed by a seven-level ordinal scale. No clinical benefit was associated with HCQ or AZ use over standard care (Cavalcanti *et al*., 2020).

A subsequent open-label, randomized clinical trial (COALITION II) at 57 centres in Brazil tested AZ versus placebo in addition to standard therapy (which included HCQ) in 447 COVID-19 patients in need of oxygen supplementation. The primary endpoint was clinical status at day 15 after randomization, assessed by a six-point ordinal scale. No significant difference in mortality or clinical status was seen between the AZ and the control group (Furtado *et al*., 2020). The Brazilian clinicians concluded from the COALITION I and II trials that it is unlikely that AZ combined with HCQ is a useful treatment option for patients admitted to hospital with COVID-19.

RECOVERY trial. In the framework of the UK RECOVERY trials, 7763 patients hospitalized with COVID-19 were included in an AZ trial. A total of 2582 patients were randomly allocated to receive AZ and 5181 patients received usual care. AZ was applied with 500 mg once per day by mouth or intravenously for 10 days. The primary outcome was 28-day all-cause mortality which was

the same in both groups (22%). No significant difference was seen in the duration of hospital stay (10 vs. 11 days) or the proportion of patients discharged from hospital alive within 28 days (69% vs. 68%) or the patients put on mechanical ventilation (25% vs. 26%). The clinicians concluded that AZ should be restricted to patients in whom there is a clear antibiotic indication for a bacterial superinfection (Recovery Collaborative Group, 2021a).

PRINCIPLE trial. The UK PRINCIPLE trial tested usual care plus AZ, usual care plus other interventions, or usual care alone in 2265 non-hospitalized older people with suspected COVID-19. The primary outcome was self-reported recovery within 28 days, hospitalization or death. Recovery was 80% in the AZ and 77% in the control group; 3% in each group had to be hospitalized for COVID-19 and none died. The clinicians found little evidence of a meaningful benefit for AZ, except a less than 1 day acceleration of recovery. The clinicians concluded that the findings do not justify the routine use of AZ in non-hospitalized COVID-19 patients, since the widespread use of antibiotics will only increase the risk of antibiotic resistance development (Principle Group, 2021).

ATOMIC trial. In the UK ATOMIC2 trial, outpatients with mild to moderate COVID-19 were randomized for ambulatory treatment with AZ ($n = 145$) or standard care ($n = 147$). No difference for clinical severity score development was seen between the two groups over the 1-month observation period. 10% vs. 12% of the outpatients in each group were hospitalized and 1% in each group needed ventilation (Hinks *et al.*, 2021).

ACTION trial. A US study randomized moderately affected COVID-19 outpatients on AZ ($n = 171$) or standard care ($n = 92$) which included HCQ. AZ treatment did not result in a greater likelihood for being symptom-free after 2 weeks (50% in both groups). By day 21, emergency department/ urgent care visits in the AZ group were significantly higher than in the placebo group (AZ 14%; placebo: 3%) and five participants in the AZ group had been hospitalized for COVID-19-related symptoms compared with none in the placebo group (Oldenburg *et al.*, 2021).

In another US study, 231 outpatients with COVID-19 were randomized on HCQ; HCQ with AZ or placebo. Primary endpoints were 14-day progression to lower respiratory tract infection and 28-day COVID-19-related hospitalization, which showed no difference between the groups. Time to viral clearance was marginally shorter in the HCQ/AZ group than in the controls (Johnston *et al.*, 2021).

Clinical trial overview: anticoagulants and organ protection

Anticoagulation

In the Iranian INSPIRATION trial, 600 COVID-19 patients admitted to ICUs were randomized on intermediate-dose anticoagulation therapy (enoxaparin, 1 mg kg^{-1} daily) or standard prophylactic anticoagulation. The primary efficacy outcome was a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days. This outcome occurred in 46% and 44% and major bleeding occurred in 2.5% and 1.4% of the enoxaparin and the standard anticoagulation group respectively. This trial does not support the routine use of anticoagulation in ICU COVID-19 patients (Inspiration Investigators, 2021). The RAPID trial, which evaluated therapeutic heparin as compared with prophylactic heparin in 465 patients who were not critically ill, revealed likewise no difference between groups for the primary endpoint (death, mechanical ventilation, ICU admission) (Sholzberg *et al.*, 2021).

A total of 615 Brazilian patients hospitalized with COVID-19 showing elevated D-dimer concentrations, a biomarker for thrombosis, were randomized to therapeutic or to prophylactic anticoagulation. Therapeutic anticoagulation was with oral rivaroxaban (15 mg daily) or subcutaneous enoxaparin (1 mg kg^{-1} twice per day) or intravenous unfractionated heparin. Prophylactic anticoagulation was standard in-hospital enoxaparin or unfractionated heparin. The primary efficacy outcome was time to death, duration of hospitalization or duration of supplemental oxygen. The primary outcome did not differ between the two groups, but the therapeutic anticoagulation groups showed significantly more bleeding events than the prophylactic anticoagulation group (8% vs. 2%). The authors concluded that routine therapeutic anticoagulation should be avoided in hospitalized COVID-19 patients with elevated D-dimer concentrations (Lopes *et al.*, 2021).

The joint evaluation of anticoagulation strategies in three platform trials (REMAP-CAP, ATTACC, ACTIV-4a) yielded a mixed picture according to disease severity. A total of 1098 critically ill COVID-19 patients treated with either therapeutic-dose anticoagulation with heparin or pharmacologic thromboprophylaxis according to local standards revealed no difference in survival (62.7% and 64.5% respectively); major bleeding occurred in 3.8% and 2.3% of the patients respectively. Therapeutic anticoagulation met the criteria of inferiority and the trial was stopped at intermediate analysis for futility (REMAP-CAP Investigators, 2021b). A different picture emerged for non-critical COVID-19 patients treated in the same format in parallel. After analysis of 2219 patients, this part of the trial was stopped for superiority of the therapeutic dose

anticoagulation which resulted in 80.2% survival compared with 76.4% survival in the thromboprophylaxis group; fatal bleeding occurred in three and one patient per group. The median value for organ support–free days did not differ between both groups. Therapeutical dose anticoagulation would thus result in 40 additional survivals in moderately ill patients when 1000 patients are treated, at the expense of seven additional major bleeding events (ATTACC Investigators, 2021). The clinicians suspected that the pathology in COVID-19 patients treated in ICU is too advanced to expect a beneficial effect of anticoagulation. The inferiority of therapeutic anticoagulation in critically ill COVID-19 patients may be linked to the observation of pathologists who detected not only microthrombosis but also alveolar haemorrhage in deceased patients, potentially explaining why therapeutic anticoagulation in severely ill patients might do harm.

Imatinib

In mice, researchers managed to infect human lung organoids transplanted as xenografts (Han *et al*., 2021). These researchers tested FDA-approved drugs for antiviral activity in this system and identified imatinib as one of four active compounds. Imatinib is an oral chemotherapy medication used to treat cancer by its activity as an ABL tyrosine kinase inhibitor. Imatinib also binds to the viral receptor ACE-2 and affects fatty acid biosynthesis, steroid biosynthesis and fatty acid metabolism (Han *et al*., 2021). Imatinib also protects against capillary leaks and might thus protect against alveolar oedema which leads to insufficient oxygen saturation in the blood of severely affected COVID-19 patients. Imatinib has also ill-characterized immunomodulatory activities (Bernal-Bello *et al*., 2021). Dutch clinicians randomized 400 hospitalized COVID-19 patients requiring supplemental oxygen to oral imatinib or placebo. The primary outcome was time to discontinuation of mechanical ventilation or supplemental oxygen which did not differ between the two groups. However, the use of imatinib was associated with lower 28-day mortality of 8% compared with 14% in controls. Since the statistical significance for a mortality difference was lost after accounting for baseline imbalances between the groups, the outcome should be interpreted with caution (Aman *et al*., 2021).

Organ protection: glifozins

When the clinical status of COVID-19 patients deteriorates, they frequently suffer multiorgan dysfunctions. Sodium-glucose transporter protein SGLT2 inhibitors, also called gliflozins as a class, inhibit reabsorption of glucose in the kidney and thus lower blood glucose levels. In large clinical trials, gliflozins were shown to confer significant cardioprotective benefit in type 2 diabetes patients. Clinicians asked in a multicentre trial enrolling 1250 hospitalized COVID-19 patients with cardiometabolic risk factors whether dapagliflozin, the first approved gliflozin worldwide, might provide organ protection compared to placebo recipients. The primary composite outcome of organ dysfunction or death occurred in 11.2% in the treatment and 13.8% in the placebo group. Also, the death rate was reduced (6.6% vs. 8.6%), but both differences were statistically not significant (Kosiborod *et al*., 2021).

Treatment guidelines

It is not easy to keep an overview of the clinical trial literature on COVID-19 drugs. To help both the clinicians and researchers, the US National Institutes of Health (NIH) published 'COVID-19 Treatment Guidelines', a comprehensive 360-page document that is regularly updated to keep pace with the publication of clinical trials in the field [COVID-19 Treatment Guidelines (nih.gov)].

With respect to antiviral therapy, the document recommends against the use of HCQ with or without AZ, against lopinavir/ritonavir and other HIV protease inhibitors, against nitazoxanide (a broad-spectrum thiazolide antiparasitic agent that is approved by FDA for the treatment of *Cryptosporidium parvum* and *Giardia duodenalis*). The NIH panel found insufficient evidence for the use of ivermectin and noted that remdesivir is the only FDA-approved drug for the treatment of COVID-19 (for overviews on antiviral drug trials in COVID-19 patients see also Brüssow, 2021).

The WHO guidelines [Therapeutics and COVID-19: living guideline (who.int)] overlap with those of the NIH; the WHO panel formulates a strong recommendation against HCQ and lopinavir/ritonavir, a recommendation against ivermectin, but differs from that of NIH by formulating a conditional recommendation against remdesivir in hospitalized COVID-19 patients.

With respect to anti-SARS-CoV-2 antibody products the NIH guidelines recommend several, but not all mabs in non-hospitalized patients at high risk of clinical progression. However, NIH recommends against convalescent plasma and against the use of dexamethasone in non-hospitalized COVID-19 patients.

With respect to immunomodulators, the NIH guidelines recommend baricitinib with dexamethasone, dexamethasone alone or tocilizumab with dexamethasone according to disease severity. The NIH panel found insufficient evidence for colchicine (in non-hospitalized patients), fluvoxamine, GM-CSF inhibitors, inhaled budesonide, IL-1 inhibitor anakinra, or Interferon-beta.

NIH treatment guidelines differ for hospitalized COVID-19 patients according to the oxygen needs of the patients. In patients without SO requirements, NIH recommends against dexamethasone while in high-risk patients without SO remdesivir might be appropriate. For patients with minimal SO need, remdesivir is an option; for those with increasing SO requirement, dexamethasone plus remdesivir could be given. COVID-19 patients who require oxygen delivery through a high flow device, dexamethasone or dexamethasone together with remdesivir should be given. If the patients show signs of systemic inflammation, baricitinib or tocilizumab (but not both together) should be added to dexamethasone with or without remdesivir. Patients in need of IMV or extracorporeal membrane oxygenation should receive dexamethasone plus tocilizumab within 24 h of admission to ICU.

The WHO treatment guidelines come to similar conclusions in formulating a strong recommendation for systemic corticosteroids in patients with severe and critical COVID-19, while giving a conditional recommendation against systemic corticosteroids in patients with non-severe COVID-19. The WHO panel also makes a strong recommendation for the IL-6 receptor blockers tocilizumab and sarilumab in severe and critical cases of COVID-19. In contrast to the NIH panel, the WHO panel suggests against administering remdesivir in addition to usual care.

Conclusion

The large overlap of the NIH and WHO guidelines indicate that we have a treatment protocol for COVID-19 patients according to disease severity, which is based on evidence from clinical trials. New evidence will certainly emerge from the hundreds of still ongoing clinical trials testing COVID-19 drugs and the guidelines will be updated accordingly in the future. However, there is still a clear need for new and more efficient drugs. Drugs with an efficiency comparable to COVID-19 vaccines are still lacking and represent a persistent challenge for drug development. New drugs that specifically target the virus or the pathology developing in COVID-19 patients are urgently needed since the repurposed drugs so far explored in the clinical drug trials against COVID-19 have only provided few drugs conferring moderate benefits in specific patient groups, namely severely affected patient subgroups, but not yet a breakthrough drug treatment in hospitalized patients or drugs for early disease states in outpatients.

Acknowledgements

References

Aman, J., Duijvelaar, E., Botros, L., Kianzad, A., Schippers, J.R., Smeele, P.J., *et al*. (2021) Imatinib in patients with severe COVID-19: a randomised, double-blind, placebo-controlled, clinical trial. *Lancet Respir Med* **9**(9): 957–968.

ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators, Lawler, P.R., Goligher, E.C., Berger, J. S., Neal, M.D., McVerry, B.J., *et al*. (2021) Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. *N Engl J Med* **385**: 790–802.

Bernal-Bello, D., Morales-Ortega, A., Isabel Farfán-Sedano, A., de Tena, J.G., Martín-López, J.V.S., *et al*. (2021) Imatinib in COVID-19: hope and caution. *Lancet Respir Med* **9**: 938–939.

Biran, N., Ip, A., Ahn, J., Go, R.C., Wang, S., Mathura, S., *et al*. (2020) Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. *Lancet Rheumatol* **2**: e603–e612.

Bozzi, G., Mangioni, D., Minoia, F., Aliberti, S., Grasselli, G., Barbetta, L., *et al*. (2021) Anakinra combined with methyl-prednisolone in patients with severe COVID-19 pneumonia and hyperinflammation: an observational cohort study. *J Allergy Clin Immunol* **147**: 561–566.e4.

Brüssow, H. (2021) Clinical trials with antiviral drugs against COVID-19: some progress and many shattered hopes. *Environ Microbiol*. https://doi.org/10.1111/1462-2920. 15769. Online ahead of print.

Cao, Y., Wei, J., Zou, L., Jiang, T., Wang, G., Chen, L., *et al*. (2020) Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): a multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol* **146**: 137–146.e3.

Cauchois, R., Koubi, M., Delarbre, D., Manet, C., Carvelli, J., Blasco, V.B., *et al*. (2020) Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. *Proc Natl Acad Sci U S A* **117**: 18951–18953.

Cavalcanti, A.B., Zampieri, F.G., Rosa, R.G., Azevedo, L.C. P., Veiga, V.C., Avezum, A., *et al*. (2020) Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N Engl J Med* **383**: 2041–2052.

Cavalli, G., De Luca, G., Campochiaro, C., Della-Torre, E., Ripa, M., Canetti, D., *et al*. (2020) Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* **2**: e325–e331.

Cavalli, G., Larcher, A., Tomelleri, A., Campochiaro, C., Della-Torre, E., De Luca, G., *et al*. (2021) Interleukin-1 and interleukin-6 inhibition compared with standard management in patients with COVID-19 and hyperinflammation: a cohort study. *Lancet Rheumatol* **3**: e253–e261.

Chen, X., Zhao, B., Qu, Y., Chen, Y., Xiong, J., Feng, Y., *et al*. (2020) Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 level in critically ill patients with coronavirus disease 2019. *Clin Infect Dis* **71**: 1937–1942.

CORIMUNO-19 Collaborative Group. (2021) Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-

ANA-1): a randomised controlled trial. *Lancet Respir Med* **9**: 295–304.

Corral-Gudino, L., Bahamonde, A., Arnaiz-Revillas, F., Gómez-Barquero, J., Abadía-Otero, J., García-Ibarbia, C., *et al*. (2021) GLUCOCOVID investigators. Methylprednisolone in adults hospitalized with COVID-19 pneumonia: an open-label randomized trial (GLUCOCOVID). *Wien Klin Wochenschr* **133**: 303–311.

Cremer, P.C., Abbate, A., Hudock, K., McWilliams, C., Mehta, J., Chang, S.Y., *et al*. (2021) Mavrilimumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID): an investigator initiated, multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Rheumatol* **3**: e410–e418.

De Luca, G., Cavalli, G., Campochiaro, C., Della-Torre, E., Angelillo, P., Tomelleri, A., *et al*. (2020) GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. *Lancet Rheumatol* **2**: e465–e473.

Deftereos, S.G., Giannopoulos, G., Vrachatis, D.A., Siasos, G.D., Giotaki, S.G., Gargalianos, P., *et al*. (2020) 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* **3**: e2013136.

Dequin, P.F., Heming, N., Meziani, F., Plantefève, G., Voiriot, G., Badié, J., *et al*. (2020) Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA* **324**: 1298–1306.

Furtado, R.H.M., Berwanger, O., Fonseca, H.A., Corrêa, T. D., Ferraz, L.R., Lapa, M.G., *et al*. (2020) 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* **396**: 959–967.

Giamarellos-Bourboulis, E.J., Netea, M.G., Rovina, N., Akinosoglou, K., Antoniadou, A., Antonakos, N., *et al*. (2020) Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe* **27**: 992–1000.e3.

Guaraldi, G., Meschiari, M., Cozzi-Lepri, A., Milic, J., Tonelli, R., Menozzi, M., *et al*. (2020) Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* **2**: e474–e484.

Guimarães, P.O., Quirk, D., Furtado, R.H., Maia, L.N., Saraiva, J.F., Antunes, M.O., *et al*. (2021) Tofacitinib in patients hospitalized with Covid-19 pneumonia. *N Engl J Med* **385**: 406–415.

Han, Y., Duan, X., Yang, L., Nilsson-Payant, B.E., Wang, P., *et al*. (2021) Identification of SARS-CoV-2 inhibitors using lung and colonic organoids. *Nature* **589**: 270–275.

Hermine, O., Mariette, X., Tharaux, P.L., Resche-Rigon, M., Porcher, R., Ravaud, P., and CORIMUNO-19 Collaborative Group. (2021) Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med* **181**: 32–40.

Hinks, T.S.C., Cureton, L., Knight, R., Wang, A., Cane, J.L., Barber, V.S., *et al*. (2021) Azithromycin versus standard care in patients with mild-to-moderate COVID-19 (ATOMIC2): an open-label, randomised trial. *Lancet Respir Med* **9**(10): 1130–1140.

Hoang, T.N., Pino, M., Boddapati, A.K., Viox, E.G., Starke, C.E., Upadhyay, A.A., *et al*. (2021) Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques. *Cell* **184**: 460–475.e21.

Huet, T., Beaussier, H., Voisin, O., Jouveshomme, S., Dauriat, G., Lazareth, I., *et al*. (2020) Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* **2**: e393–e400.

INSPIRATION Investigators, Sadeghipour, P., Talasaz, A.H., Rashidi, F., Sharif-Kashani, B., Beigmohammadi, M.T., *et al*. (2021) Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extra-corporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. *JAMA* **325**: 1620–1630.

Johnston, C., Brown, E.R., Stewart, J., Karita, H.C.S., Kissinger, P.J., Dwyer, J., *et al*. (2021) Hydroxychloroquine with or without azithromycin for treatment of early SARS-CoV-2 infection among high-risk outpatient adults: a randomized clinical trial. *EClinicalMedicine* **33**: 100773.

Kalil, A.C., Patterson, T.F., Mehta, A.K., Tomashek, K.M., Wolfe, C.R., Ghazaryan, V., *et al*. (2021) Baricitinib plus Remdesivir for hospitalized adults with Covid-19. *N Engl J Med* **384**: 795–807.

Kosiborod, M.N., Esterline, R., Furtado, R.H.M., Oscarsson, J., Gasparyan, S.B., Koch, G.G., *et al*. (2021) Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol* **9**: 586–594.

Kyriazopoulou, E., Huet, T., Cavalli, G., Gori, A., Kyprianou, M., Pickkers, P., *et al*. (2021b) Effect of anakinra on mortality in patients with COVID-19: a systematic review and patient-level meta-analysis. *Lancet Rheumatol* **3**(10): e690–e697. https://doi.org/10.1016/S2665-9913(21)00216-2.

Kyriazopoulou, E., Panagopoulos, P., Metallidis, S., Dalekos, G.N., Poulakou, G., Gatselis, N., *et al*. (2021a) An open label trial of anakinra to prevent respiratory failure in COVID-19. *Elife* **10**: e66125.

Lenze, E.J., Mattar, C., Zorumski, C.F., Stevens, A., Schweiger, J., Nicol, G.E., *et al*. (2020) Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA* **324**: 2292–2300.

Lescure, F.X., Honda, H., Fowler, R.A., Lazar, J.S., Shi, G., Wung, P., *et al*. (2021) Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* **9**: 522–532.

Lopes, R.D., de Barros, E., Silva, P.G.M., Furtado, R.H.M., Macedo, A.V.S., Bronhara, B., *et al*. (2021) Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet* **397**: 2253–2263.

Marconi, V.C., Ramanan, A.V., de Bono, S., Kartman, C.E., Krishnan, V., Liao, R., *et al*. (2021) Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med*. Online ahead of print.

Oldenburg, C.E., Pinsky, B.A., Brogdon, J., Chen, C., Ruder, K., Zhong, L., *et al*. (2021) Effect of oral azithromycin vs placebo on COVID-19 symptoms in outpatients with SARS-CoV-2 infection: a randomized clinical trial. *JAMA* **326**: 490–498.

Osuchowski, M.F., Winkler, M.S., Skirecki, T., Cajander, S., Shankar-Hari, M., *et al*. (2021) The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. *Lancet Respir Med* **9**: 622–642.

Pinzón, M.A., Ortiz, S., Holguín, H., Betancur, J.F., Cardona Arango, D., Laniado, H., *et al*. (2021) Dexamethasone vs methylprednisolone high dose for Covid-19 pneumonia. *PLoS One* **16**: e0252057.

Pontali, E., Volpi, S., Signori, A., Antonucci, G., Castellaneta, M., Buzzi, D., *et al*. (2021) Efficacy of early anti-inflammatory treatment with high doses of intravenous anakinra with or without glucocorticoids in patients with severe COVID-19 pneumonia. *J Allergy Clin Immunol* **147**: 1217–1225.

Prado Jeronimo, C.M., Farias, M.E.L., Val, F.F.A., Sampaio, V.S., Alexandre, M.A.A., Melo, G.C., *et al*. (2021) 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* **72**: e373–e381.

PRINCIPLE Trial Collaborative Group. (2021) Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK(PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet* **397**: 1063–1074.

Rabbani, A.B., Parikh, R.V., and Rafique, A.M. (2020) Colchicine for the treatment of myocardial injury in patients with coronavirus disease 2019 (COVID-19)-an old drug with new life? *JAMA Netw Open* **3**: e2013556.

Ramakrishnan, S., Nicolau, D.V., Jr., Langford, B., Mahdi, M., Jeffers, H., Mwasuku, C., *et al*. (2021) Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. *Lancet Respir Med* **9**: 763–772.

Ranjbar, K., Moghadami, M., Mirahmadizadeh, A., Fallahi, M.J., Khaloo, V., Shahriarirad, R., *et al*. (2021) Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial. *BMC Infect Dis* **21**: 337.

Rashad, A., Mousa, S., Nafady-Hego, H., Nafady, A., and Elgendy, H. (2021) Short term survival of critically ill COVID-19 Egyptian patients on assisted ventilation treated by either dexamethasone or tocilizumab. *Sci Rep* **11**: 8816.

RECOVERY Collaborative Group. (2021a) Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* **397**: 605–612.

RECOVERY Collaborative Group. (2021b) Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* **397**: 1637–1645.

RECOVERY Collaborative Group, Horby, P., Lim, W.S., Emberson, J.R., Mafham, M., Bell, J.L., *et al*. (2021) Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* **384**: 693–704.

RECOVERY Group. (2021) Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet Respir Med* **S2213-2600**(21): 00435–5. https://doi.org/10.1016/S2213-2600(21)00435-5.

REMAP-CAP Investigators, ACTIV-4a Investigators, ATTA CC Investigators, Goligher, E.C., Bradbury, C.A., McVerry, B.J., *et al*. (2021a) Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. *N Engl J Med* **385**: 777–789.

REMAP-CAP Investigators, Angus, D.C., Derde, L., Al-Beidh, F., Annane, D., Arabi, Y., *et al*. (2020) 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* **324**: 1317–1329.

REMAP-CAP Investigators, Gordon, A.C., Mouncey, P.R., Al-Beidh, F., Rowan, K.M., Nichol, A.D., *et al*. (2021b) Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* **384**: 1491–1502.

Rosas, I.O., Bräu, N., Waters, M., Go, R.C., Hunter, B.D., Bhagani, S., *et al*. (2021) Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. *N Engl J Med* **384**: 1503–1516.

Russell, C.D., Millar, J.E., and Baillie, J.K. (2020) Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* **395**: 473–475.

Salama, C., Han, J., Yau, L., Reiss, W.G., Kramer, B., Neidhart, J.D., *et al*. (2021) Tocilizumab in patients hospitalized with Covid-19 pneumonia. *N Engl J Med* **384**: 20–30.

Salvarani, C., Dolci, G., Massari, M., Merlo, D.F., Cavuto, S., Savoldi, L., and RCT-TCZ-COVID-19 Study Group. (2021) Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med* **181**: 24–31.

Sholzberg, M., Tang, G.H., Rahhal, H., AlHamzah, M., Baumann, K.L., Ní Áinle, F., *et al*. (2021) Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. *BMJ*, **375**: n2400.

Soin, A.S., Kumar, K., Choudhary, N.S., Sharma, P., Mehta, Y., Kataria, S., *et al*. (2021) Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multi-centre, randomised, controlled, phase 3 trial. *Lancet Respir Med* **9**: 511–521.

Somers, E.C., Eschenauer, G.A., Troost, J.P., Golob, J.L., Gandhi, T.N., Wang, L., *et al*. (2021) Tocilizumab for treatment of mechanically ventilated patients with COVID-19. *Clin Infect Dis* **73**(2): e445–e454.

Stebbing, J., and Lauschke, V.M. (2021) JAK inhibitors - more than just glucocorticoids. *N Engl J Med* **385**: 463–465.

Stebbing, J., Sánchez Nievas, G., Falcone, M., Youhanna, S., Richardson, P., Ottaviani, S., *et al.* (2021) JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality. *Sci Adv* **7**: eabe4724.

Stone, J.H., Frigault, M.J., Serling-Boyd, N.J., Fernandes, A. D., Harvey, L., Foulkes, A.S., *et al.* (2020) Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med* **383**: 2333–2344.

Tardif, J.C., Bouabdallaoui, N., L'Allier, P.L., Gaudet, D., Shah, B., Pillinger, M.H., *et al.* (2021) Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. *Lancet Respir Med* **9**(8): 924–932.

Titanji, B.K., Farley, M.M., Mehta, A., Connor-Schuler, R., Moanna, A., *et al.* (2021) Use of baricitinib in patients with moderate to severe coronavirus disease 2019. *Clin Infect Dis* **72**: 1247–1250.

Tomazini, B.M., Maia, I.S., Cavalcanti, A.B., Berwanger, O., Rosa, R.G., Veiga, V.C., *et al.* (2020) Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA* **324**: 1307–1316.

Wagner, C., Griesel, M., Mikolajewska, A., Mueller, A., Nothacker, M., Kley, K., *et al.* (2021) Systemic corticosteroids for the treatment of COVID-19. *Cochrane Database Syst Rev* **8**: CD014963. https://doi.org/10.1002/14651858. CD014963.

WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne, J.A.C., Murthy, S., Diaz, J.V., Slutsky, A.S., Villar, J., *et al.* (2020) Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* **324**: 1330–1341.

Xu, X., Han, M., Li, T., Sun, W., Wang, D., Fu, B., *et al.* (2020) Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A* **117**: 10970–10975.

Yu, L.M., Bafadhel, M., Dorward, J., Hayward, G., Saville, B. R., Gbinigie, O., *et al.* (2021) Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK(PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet* **398**: 843–855.