FOCUSED REVIEW

Repurposing Existing Drugs for the Treatment of COVID-19

Hugo Farne, Kartik Kumar, Andrew I. Ritchie, Lydia J. Finney, Sebastian L. Johnston, and Aran Singanayagam

National Heart and Lung Institute, Imperial College London, London, United Kingdom

ORCID IDs: 0000-0003-2556-3953 (H.F.); 0000-0001-9849-0033 (A.S.).

Abstract

The rapid global spread and significant mortality associated with the coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection has spurred an urgent race to find effective treatments. Repurposing existing drugs is a particularly attractive approach as pharmacokinetic and safety data already exist; thus, development can leapfrog straight to clinical trials of efficacy, generating results far more quickly than *de novo* drug development. This review summarizes the state of play for the principle drugs identified as candidates to be repurposed for treating COVID-19 grouped by broad mechanism of action: antiviral, immune enhancing, and antiinflammatory or immunomodulatory. Patient selection, particularly with regard to disease stage, is likely to be key. To date, only dexamethasone and remdesivir have been shown to be effective, but several other promising candidates are in trials.

Keywords: coronavirus; COVID-19; severe acute respiratory syndrome coronavirus 2; therapeutics

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Correspondence and requests for reprints should be addressed to Aran Singanayagam, M.B. Ch.B., Ph.D., National Heart and Lung Institute, Norfolk Place, London W2 1PG, UK. E-mail: a.singanayagam@imperial.ac.uk.

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Introduction

Coronavirus disease (COVID-19) is the illness resulting from syndrome coronavirus 2 (SARS-CoV-2), a highly pathogenic coronavirus showing some similarities with Middle East respiratory syndrome (MERS)-CoV and SARS-CoV. Unlike the previous MERS and SARS outbreaks, the 2019/20 outbreak has been declared a pandemic by the World Health Organization owing to high infectivity and case fatality rates. Most countries have introduced unprecedented emergency measures to support the medical response, at significant cost to their citizens and economies. Efficacious treatment, prevention of spread, and vaccine development are global imperatives.

Vaccines and antiviral therapies developed *de novo* for SARS-CoV-2 are likely to take at least 12–18 months to become clinically available. Repurposing existing pharmacological therapies that already have safety data can be achieved far more quickly and is therefore a major focus of current research. This review discusses the principal therapies that are targets of repurposing efforts for COVID-19, summarizing the theoretical basis and available evidence for each. Where it exists, we focus on human clinical data in SARS-CoV-2 infection, but in the absence of those data, evidence is drawn from the other epidemic respiratory viruses including influenza, SARS-CoV, and MERS-CoV. The volume of literature and research on COVID-19 is such that it is not possible to discuss all existing drugs that have been proposed as treatment options; thus, we have focused on agents where there was clear supportive evidence to draw from. Treatment of complications such as fever, thromboses, acute respiratory distress syndrome, and secondary bacterial infections are outside the scope of this review and are not directly addressed.

Aims and Timing of Treatment

Studies of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) suggest that most cases are initiated by relatively low virus loads and have a benign course, with symptoms ranging from asymptomatic to mild or moderate disease of variable duration. More severe disease is associated with higher viral load at presentation (1, 2), with fever and cough the most typical symptoms (3). This is followed by a second

phase likely characterized by virus-load–driven inflammatory response and manifests as pneumonia, hypoxemia, and fever, occurring 7–8 days from symptom onset, when most patients present to the hospital (4, 5). A subgroup progress to a third phase with an overwhelming proinflammatory response (again likely virus-load driven, with severe disease associated with delayed viral clearance up until at least Day 10) (1) resulting in acute respiratory distress syndrome (ARDS), usually around Day 10 (4). Nasopharyngeal viral load peaks in the early stages in mild disease, but tends to be higher in severe disease and to persist for longer (1), suggesting that antiviral or immune-boosting therapies are likely to be most beneficial in this early phase (it is well established from previous studies of antiviral therapies in respiratory disease that early intervention results in better outcomes). However, recent results with the antiviral remdesivir indicate that antivirals administered even as late as at hospitalization can be effective (6, 7). Equally immunosuppressive therapies may have deleterious effects if given when viral loads are high and the magnitude of the inflammatory response is appropriate. A suggestion that this is the case is seen in the trend toward increased mortality in patients not receiving oxygen therapy treated with dexamethasone (risk ratio [RR], 1.22; 95% confidence interval [95% CI], 0.93–1.61) (8). As the disease progresses to its most severe form, hyperinflammation is undoubtedly present, and thus, in those who develop ARDS, therapeutics aimed at attenuating the inflammatory response may be effective. Correspondingly dexamethasone improves survival in those requiring oxygen and particularly in those requiring mechanical ventilation, with a greater mortality benefit in those with a longer duration of symptoms (Figure 1) (8).

Antiviral Therapies

Remdesivir

Remdesivir was developed to treat Ebola, another single-stranded RNA virus, during the recent epidemic in West Africa. It acts as an adenosine analog to interfere with viral RNA-dependent RNA-polymerase (RdRp) and induce premature or delayed RNA chain termination (9), while evading viral exoRNase activity (10). *In vitro*, it has antiviral activity against respiratory viral pathogens including SARS-CoV-2 (11). Similar protective effects are seen *in vivo* in SARS-CoV– and Middle East respiratory syndrome (MERS-CoV)–infected mice with reduced airway inflammation and lung function decline (12, 13). Importantly, the efficacy of postexposure treatment depends on when the drug is given relative to peak viral replication and airway epithelial damage (11, 12).

A case series of 61 hospitalized patients treated with remdesivir off license reported a clinical improvement in 36 out of 53 patients with sufficient data to analyze, although without a control group it is difficult to interpret these findings (14). An initial randomized controlled trial (RCT) was inconclusive, with a nonsignificant trend toward reduced time to clinical improvement favoring remdesivir (15). However, this trial was underpowered, with recruitment ending prematurely at 237 out of an intended 453 patients following the end of the outbreak in Wuhan. A subsequent RCT enrolling 1,063 patients found accelerated recovery in patients receiving remdesivir (median time to recovery 11 d vs. 15 d on placebo; $P < 0.001$) (7). In addition, there was a trend toward improved survival at Day 14 (7.1% with remdesivir vs. 11.9% placebo; hazard ratio [HR], 0.7; 95% CI, 0.47–1.04). Subgroup analysis found no benefit in those on high-flow oxygen or noninvasive ventilation, or invasive ventilation, suggesting that antivirals such as remdesivir will be of limited efficacy in late disease where the pathology is likely inflammatory in origin. It should be noted the study was reported early and full outcomes (e.g., 28-d mortality) were therefore only available for 731/1,063 (69%) patients; further follow-up data are awaited.

Favipiravir

Favipiravir acts as a purine analog to also disrupt RdRp and is licensed to treat influenza in Japan (16). It is effective *in vitro* against a range of RNA viruses including SARS-CoV-2 (11). In mice, favipiravir improves survival in influenza A infection (17).

An open-label nonrandomized trial in China found a significantly shorter time to viral clearance (4 d [interquartile range (IQR), 2.5–9] vs. 11 d [IQR, 8–13]) and greater improvement in chest radiographic appearances in patients with SARS-CoV-2 treated with favipiravir/interferon (IFN)-α ($n = 35$) compared with lopinavir/ritonavir/IFN-α ($n = 45$) (18).

Lopinavir/Ritonavir ± Ribavirin

Lopinavir (LPV) and ritonavir (RTV) are protease inhibitors that are prescribed in combination form (Kaletra; AbbVie) for the treatment of human immunodeficiency virus. Lopinavir is thought to inhibit coronavirus proteases that cleave viral polyprotein to lead to the formation of RdRp; ritonavir boosts the bioavailability of lopinavir by inhibiting cytochrome P450. Ribavirin is a guanosine analog, terminating RdRp-mediated viral RNA chain elongation (19). In murine MERS-CoV infection, prophylactic LPV/RTV-IFN-β modestly reduced viral load compared with remdesivir, but treatment after infection showed no significant effect on viral load, lung hemorrhage, or acute lung injury (13).

Numerous human studies have assessed LPV/RTV, with or without ribavirin, as a treatment for COVID-19. A retrospective cohort study observed no difference in viral shedding or survival for 41/191 patients treated with LPV/RTV (20). Similarly, a larger ($n = 199$) open-label RCT found LPV/RTV did not affect time to clinical improvement (HR for clinical improvement, 1.24; 95% CI, 0.90–1.72) (21). However a modified intention-to-treat analysis that excluded three patients who died within 24 hours of randomization found time to clinical improvement was a median 1 day shorter in the treatment group (15 d vs. 16 d; HR, 1.39; 95% CI, 1.00–1.91). There was no difference in viral loads, with 42% of patients positive for SARS-CoV-2 at Day 28 suggesting at best incomplete antiviral effects, and higher gastrointestinal adverse effects in the treatment group. Several limitations may have impacted the results including higher baseline viral loads in the treatment group, the possibility of confounding from additional clinical interventions (e.g., corticosteroids), and delayed time to intervention (enrollment was a median 13 d after symptom onset). A smaller ($n = 86$) open-label RCT comparing LPV/RTV, umifenovir, and a control group on no antiviral found no evidence of benefit in terms of time to viral clearance, antipyresis, cough alleviation, or improvement of chest computed tomography (22).

To date, only one open-label RCT has assessed the combination of ribavirin with LPV/RTV, with IFN-β additionally given if patients had a symptom history of <7 days (23). Triple therapy was associated with

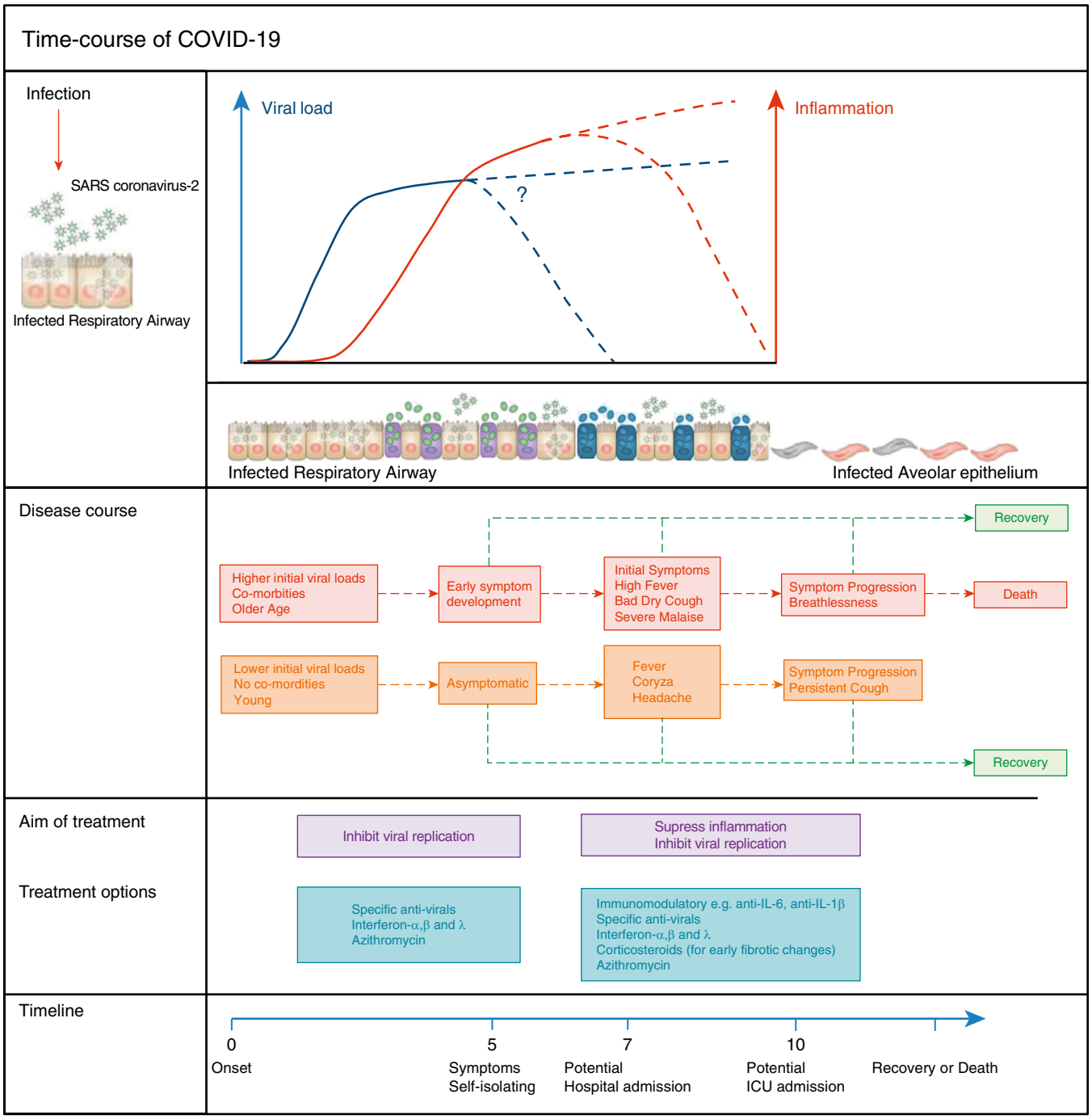

Figure 1. Possible timing of drug treatments by disease phase. Following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory viral load is likely to increase over the first 7 days before stabilizing or starting to decrease. Interferon responses and airway inflammatory response is delayed, with early symptoms typically occurring 5 days following infection. In 80% of people affected, symptoms are mild and patients recover without further medical intervention. However, a subgroup of patients experience symptoms of an excessive and dysregulated inflammatory response to viral infection presenting with breathlessness, hypoxia, and symptoms of viral pneumonia at Day 7. This excessive inflammatory response may continue to progress to acute respiratory distress syndrome, leading to the need for mechanical ventilation or death. Treatments aimed at preventing viral replication such as exogenous interferons, hydroxychloroquine, azithromycin, or specific antivirals are most likely to be effective in the early stages of disease, when viral load is increasing, before hospital admission. In contrast, treatments aiming to reduce the excessive inflammatory response to viral infection such as corticosteroids and immunomodulatory drugs are more likely to be effective in the later stages of disease following hospital admission. COVID-19 = coronavirus disease.

Table 1. Key points

- Vaccines and antiviral therapies developed *de novo* for SARS-CoV-2 are likely to take at least 12–18 mo to become clinically available.
- Repurposing licensed drugs with existing safety data can be achieved far more quickly.
- Timing of treatment is likely to be key: antivirals should be more effective if given early; antiinflammatory treatments if given later in the disease course.
- Currently, the only drugs with RCT data supporting their use in COVID-19 are:
  dexamethasone, which reduced mortality in patients requiring oxygen and/or mechanical ventilation; and
  remdesivir, which shortened time to recovery particularly in milder cases (probably earlier in the disease course).
- It is important that, despite the urgency, clinical trial research is conducted in line with accepted scientific principles. Poorly designed trials consume research resources and time without advancing our understanding, therefore unethically exposing patients to unproven therapies.
- A large number of clinical trials are currently in progress; readers are advised to consult the most up-to-date guidelines given the pace of change.

Definition of abbreviations: COVID-19 = coronavirus disease; RCT = randomized controlled trial; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

reductions in time to viral clearance, normalization of vital observations, and length of hospital stay compared with LPV/RTV. In a subgroup analysis, these findings were only true of those treated within 7 days of symptom onset. This trial only enrolled patients with mild or moderate disease (there was no mortality in either group, $n = 127$), so it is unclear whether the findings apply to severe patients.

Chloroquine and Hydroxychloroquine

Chloroquine has long been used as an antimalarial agent. The emergence of chloroquine-resistant strains of *Plasmodium* prompted the development of chloroquine analogs including hydroxychloroquine. Hydroxychloroquine, owing to its immunomodulatory properties, is used in the treatment of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. It is less toxic in animals than chloroquine (24) (Table 1).

Various mechanisms may underlie the antiviral properties of chloroquine and its analogs. Following protonation and subsequent accumulation of these drugs inside lysosomes, there is a rise in lysosomal pH, which interferes with subsequent intracellular viral trafficking (25). Chloroquine impairs autophagosome fusion with lysosomes (26) and inhibits terminal glycosylation of angiotensin-converting enzyme 2 on the cell surface, required for viral entry (27). Additionally, hydroxychloroquine interferes with both Toll-like receptor signaling (due to endosomal pH changes) (28) and cyclic guanosine monophosphate–adenosine monophosphate synthase (29), both of which result in diminished downstream production of type-I IFNs (30) and other cytokines, which may reduce the risk of a "cytokine storm." (31) *In vitro*, hydroxychloroquine has superior activity against SARS-CoV-2 infection compared with chloroquine, when administered either before or after infection (32). Thus, it was hypothesized that chloroquine or hydroxychloroquine might be effective both early and late in the disease owing to their antiviral and antiinflammatory effects, respectively.

Both chloroquine and hydroxychloroquine are being assessed as treatments for SARS-CoV-2 in various clinical trials. There are no published data on chloroquine, despite reports in the media and inclusion in various national guidelines. However, published trials of hydroxychloroquine have been the subject of some controversy, with a small ($n = 26$) but well-publicized open-label trial in France suggesting benefit (33), although many have questioned these results because of major methodological flaws, including exclusion of six patients in the treatment arm, a lack of randomization, possible confounders including variable viral loads at enrollment, and selection bias in the administration of azithromycin to a subset of patients. A separate pilot study of 30 patients randomized to hydroxychloroquine or conventional treatment found no significant differences in time to viral clearance, resolution of fever, or radiological progression (34). A further open-label RCT of 150 hospitalized patients comparing hydroxychloroquine with standard of care showed no difference in viral clearance at 28 days but did show an improvement in symptom burden and reduction in C-reactive protein at 28 days (35). However, this was offset by a significantly higher risk of adverse events—30% in the hydroxychloroquine group versus 8.8% in the standard of care group ($P = 0.001$).

A retrospective analysis of 368 patients treated with hydroxychloroquine monotherapy, hydroxychloroquine and azithromycin, or standard care found no difference in the need for mechanical ventilation but an increased risk of all-cause mortality in the hydroxychloroquine group (HR, 2.61; 95% CI, 1.10–6.17; $P = 0.03$) (36). A very large ($n = 96{,}032$) observational study of chloroquine and hydroxychloroquine with or without a macrolide was published in *The Lancet*, reporting an increase in mortality with treatment, but has since been retracted over concerns regarding the integrity of the source data (37). A press release from the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial has reported no benefit of hydroxychloroquine (28-d mortality 25.7% vs. 23.5% usual care; HR, 1.11; 95% CI, 0.98–1.26; $P = 0.10$); full results are awaited (38). Treatment is not without risk: serious adverse effects including QT prolongation with potentially fatal cardiac arrhythmia have been reported in patients treated with both drugs (39). More robust data are now needed before these drugs can be given in COVID-19.

Promoters of the Innate Antiviral Response

Evidence for Antiviral Immune Suppression in COVID-19

IFNs, specifically type-I (IFN-α and-β) and -III (IFN-λ), are a key component of the host innate defense against viruses. Upon viral infection, specific molecular patterns that are frequently expressed by viruses are detected by host pattern recognition receptors to induce secretion of IFNs. These then mediate a gene expression program via hundreds of IFN-stimulated genes with pleiotropic antiviral effects (40). Both SARS-CoV-2 and SARS-CoV can delay and/or reduce type-I IFN signaling and thus replicate to high viral titers (41, 42). This impaired IFN response is a direct consequence of strategies evolved by the virus to evade host immune defenses. These include mechanisms to counteract IFN induction, for example, sequestering viral dsRNA within double membrane vesicles to escape detection, and to disrupt IFN signaling, for example, proteolytic degradation of the type-I IFN receptor, blocking STAT1 phosphorylation (43).

IFN deficiencies may partly explain the striking high mortality in the elderly in

COVID-19 (44). Researchers comparing SARS-CoV infection in aged and young adult macaques found more pathology in the older animals despite similar viral titers, with decreased expression of IFN-β and increased expression of inflammatory genes in lung tissue (45). Treating aged macaques with IFN-α 1 and 3 d after infection significantly improved lung pathology and outcomes, with corresponding differences in proinflammatory gene transcripts. Prophylactic or early-disease-phase treatment with IFN has therefore been proposed.

Exogenous Interferon Therapy

Although IFNs were discovered in 1957, when Lindenmann and Isaacs observed that chicken embryos stimulated with heat-killed viruses released a soluble product that "interfered" with influenza virus replication, it took the advent of recombinant DNA production techniques to enable sufficient IFNs to be produced to assess their therapeutic potential. Initial studies found intranasal IFN-α reduced infection rates, symptoms, and viral loads both following experimental infection with respiratory viruses (rhinoviruses, coronaviruses, and influenza) and when given as prophylaxis for naturally occurring infections (46). However, treatment was associated with nasal erosions and bleeding, which led to these therapies being abandoned, although IFNs were subsequently licensed for the treatment of chronic hepatitis B and C.

More recently, investigators assessed whether inhaled IFN-β given to patients with asthma within 24 hours of cold symptoms would improve their asthma control (47). Although the primary endpoint was not met, a prespecified subgroup analysis found reduced symptom scores and improved lung function in those with moderately severe asthma. Timing may be key: a recent *ex vivo* study found effects only when treating macrophages and bronchial epithelial cells with IFN-β before, but not after, stimulation with influenza (48).

In vitro and *in vivo* studies of SARS-CoV and MERS-CoV have found high-dose type-I and -III IFN to be effective (43). A single pilot clinical trial in SARS with 22 patients indicated that the addition of IFN-α to corticosteroids was associated with improved oxygen saturations, resolution of lung abnormalities on imaging, and a trend toward reduced need for mechanical ventilation (49). However, the IFN-α group also received higher doses of corticosteroids and the numbers are too small to draw firm conclusions. IFN-α was given at a median 8 days after symptom onset, implying beneficial effects even when given relatively late after infection, consistent with a study of SARS-infected macaques treated with IFN-α2β (50). This is of particular interest because it suggests that exogenous IFNs may still be beneficial at the time patients present to the hospital.

A recent *in vitro* study suggests SARS-CoV-2 may be more susceptible to IFN-α treatment than SARS-CoV, which the authors attributed to differences in two of the viral proteins that antagonize IFN (51). Several trials of recombinant IFN therapy are in progress. IFN treatment will need to be carefully balanced against the potential for these drugs to promote pulmonary vascular disease (52).

Azithromycin

Azithromycin is a macrolide antibiotic that possesses additional properties that may support its use in viral infections, including induction of antiviral IFNs. Azithromycin doubles levels of antiviral type-I and type-III IFN released from virus-infected bronchial epithelial cells, a property not seen with the macrolides erythromycin and telithromycin or roughly half of 225 novel macrolides studied (53, 54). Macrolides also possess antiinflammatory properties (55) that could ameliorate COVID-19 and are antibiotic and thus could help prevent secondary bacterial infection. A drug screen preprint has suggested azithromycin possesses antiviral activity against SARS-CoV-2 (56), although this has not been seen in other drug screening studies (57).

Two studies assessing the effectiveness of azithromycin when added to oseltamivir in patients with influenza showed evidence of clinical benefit (58, 59). Conversely, analysis of a retrospective multicenter cohort of patients with MERS treated with macrolides found no improvement in 90-day mortality or viral clearance (60). However, this study only included critically ill patients with MERS, the majority of whom were not treated with a macrolide until after admission to intensive care, and 39% of whom received a macrolide other than azithromycin. As with chloroquine and hydroxychloroquine, azithromycin is associated with serious adverse effects, also including QT prolongation and cardiac arrhythmias, and in the absence of evidence of benefit, should not be given outside of a clinical trial.

Exogenous Anti–SARS-CoV-2 Antibody

The transfer of antibodies from a recovered patient to a diseased one, so-called passive immunity, received revived interest during the Ebola epidemic. Convalescent plasma or sera are attractive options but logistically challenging to source at scale. A single RCT found no benefit in the primary outcome of time to clinical improvement, although a statistically significant reduction was seen in a subgroup with severe but non–life-threatening disease (61). There was also a trend toward significantly reduced 28-day mortality that requires further corroboration. However, this study was underpowered, terminating early with 103 out of the planned 200 patients owing to containment of COVID-19 in China. The only other evidence comes from isolated reports of the use of convalescent plasma in COVID-19, with a meta-analysis finding seven case series and one prospective single-arm study with a total of 32 participants (62). With small numbers, a lack of control groups, and a high risk of bias, no conclusions could be drawn about efficacy, and although serious adverse events were infrequent, they were not absent. Forty-seven studies are ongoing, including 22 RCTs.

Immunomodulatory and Antiinflammatory Drugs

Immunosuppressive Therapies

The rationale for using immunomodulatory therapies in SARS-CoV-2 is to target hyperinflammation in the later stages of COVID-19. In clinical studies of SARS-CoV infection, serum levels of proinflammatory cytokines (IFN-γ, IL-1, IL-6, IL-12, and TGFβ) and chemokines (CCL2, CXCL8, CXCL9, and CXCL10) were significantly higher in plasma from patients with severe disease compared with those with moderate disease (63, 64). High levels of the proinflammatory cytokines IL-6, IL-8, and IL-1β and chemokines CCL2, CCL5, CXCL10, and CCL3 were associated with an increased risk of ARDS (64, 65).

Accordingly, an early study of patients infected with SARS-CoV-2 with ARDS requiring ICU admission exhibited higher serum levels of IL-2, IL-7, IL-10, G-CSF, MCP-1, MIP-1a, TNF, and CXCL10 compared with patients not requiring ICU care (4), while an elevated ferritin and serum IL-6 have been associated with increased risk of mortality (20). This cytokine profile has been likened to secondary hemophagocytic lymphohistiocytosis, a hyperinflammatory syndrome that can be caused by viral infections and frequently results in ARDS (66). In addition, many of the clinical features and laboratory findings of patients with severe COVID-19 meet the criteria for cytokine storm syndrome (CSS) (67). Consequently, immunomodulators and compounds targeting specific inflammatory cytokines are being pursued as potential treatments. However, it should be noted that no report discussing CSS in SARS, MERS, or COVID-19 has actually measured virus load in the lung, so whether CSS is purely driven by high lung virus loads has not been properly investigated to date.

Anti–IL-6 (Tocilizumab, Siltuximab)

Blockade of IL-6 with the humanized monoclonal antibody tocilizumab is currently U.S. Food and Drug Administration approved for use in cytokine release syndrome as well as rheumatoid arthritis and systemic juvenile idiopathic arthritis. As a result, there is substantial interest in IL-6 blockade as a treatment in COVID-19 resulting in off-license use.

Numerous case series of patients treated with tocilizumab off license have been published with mixed results (68–75). Certainly tocilizumab is effective in reducing fever and inflammatory markers, but whether clinical outcomes are meaningfully different will require an RCT, of which several are in progress. Another anti–IL-6 monoclonal antibody, siltuximab, has been used in 21 ventilated patients with COVID-19 on compassionate use grounds. An improvement was seen in seven patients, with nine patients stabilizing. However, five (24%) experienced worsening in their condition (76).

IL-1 Receptor Antagonist (Anakinra)

Binding of SARS-CoV-2 also activates pro–IL-1β, leading to inflammasome activation and production of IL-1β (77), which in turn mediates influx of inflammatory cells, resulting in lung inflammation and eventually fibrosis. Anti–IL-1 therapy with the recombinant IL-1RA (IL-1 receptor antagonist) protein anakinra has previously been shown to reduce mortality in patients with sepsis-related hyperinflammation (78). Three small case series in COVID-19 from Greece, France, and Italy with between five and nine patients have now been published (79–81), but as for anti–IL-6 therapies, it is hard to draw conclusions in the absence of a control group randomized to placebo. RCTs are ongoing.

Corticosteroids

The use of systemic corticosteroids to suppress SARS-CoV-2–induced lung inflammation has been advocated to prevent and/or treat ARDS, but there is a risk that they inhibit immune responses and impair pathogen clearance. Indeed, in severe influenza, corticosteroids are associated with increased mortality (82). Initial World Health Organization guidance on COVID-19 cautioned against the routine use of systemic corticosteroids, except for specific indications, such as septic shock or an exacerbation of underlying airways disease (83).

That has changed with the recent results of a large ($n = 6{,}425$) RCT of dexamethasone (8). Twenty-eight day mortality was reduced with dexamethasone in the overall cohort (21.6% vs. 24.6% usual care; RR, 0.83; 95% CI, 0.74–0.92; $P < 0.001$). Strikingly, dexamethasone reduced mortality by 35% in those on mechanical ventilation (29.0% vs. 40.7%; RR, 0.65; 95% CI, 0.48–0.88; $P = 0.003$) and by 20% in those treated with oxygen (21.5% vs. 25.0%; RR, 0.80; 95% CI, 0.67–0.96; $P = 0.0021$) but with a trend toward worse survival in mild cases not requiring oxygen (17.0% vs. 13.2%; RR, 1.22; 95% CI, 0.93–1.61; $P = 0.14$). As well as demonstrating the benefit of dexamethasone, this result reinforces the importance of RCTs: previous observational studies in COVID-19 had found associations between corticosteroid use and disease severity and/or death, which now appears to reflect a greater propensity to treat with corticosteroids in severe disease (84–86).

Conclusions

Currently, there is only RCT evidence in COVID-19 to support dexamethasone in patients requiring at least oxygen therapy, and remdesivir for shortening time to recovery, although remdesivir appears only to be beneficial if given early in the disease process. A large number of clinical trials are currently in progress assessing a variety of existing antiviral, immune-enhancing, immunomodulatory, and immunosuppressive treatments. Early results are expected in the coming weeks, months ahead of vaccines and newly developed antivirals. Readers are advised to consult the most up-to-date guidelines given the pace of change.

Although there is a place for the use of drugs on compassionate grounds and experience sharing through reports of case series, it is important that, despite the urgency, clinical trial research is conducted in line with accepted scientific principles (as set out in various guidelines) (87, 88). Poorly designed trials consume research resources and time without advancing our understanding of whether a treatment is effective and as such represent unethical exposure of patients to unproven therapies. National and international coordination of trials will also be important, both to ensure a unified effort and to rationalize the number of trials, thereby reducing the risk of a type-I error. Governments and health service providers must also maintain a focus on preventive measures, both nonpharmacological and vaccines. Ultimately, treatments will be needed as social distancing measures, which cannot go on indefinitely, are finally lifted. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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