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Covid-19 Treatment: A Narrative Review of the Research and Evidence Thus Far

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Abstract

The emergence of the novel SARS-CoV-2 virus has led to an unprecedented global pandemic with a high degree of morbidity and mortality. Treatment regimens around the world have been varied both in their drug combinations and the levels of evidence behind them. Drugs that have been used for other immune modulating purposes are being re-trialled to try to combat this disease, with data showing far from conclusive results. We will examine the most common treatment strategies, including the rationale and evidence behind their use. Our conclusion, which is becoming universally realised amongst researchers, is that much more evidence is required to prove clinical efficacy of many of the currently available treatments.

Abbreviations

TTR: Time to Recovery; HR: Hazard Ratio; RR: Risk Ratio; CI: Confidence Interval; RCT: Randomised Controlled Trial; ARDS: Acute Respiratory Distress Syndrome; LMWH: Low Molecular Weight Heparin; HFNO: High Flow Nasal Oxygen; CPAP: Continuous Positive Airway Pressure; MHRA: Medicines & Health Regulatory Agency; FDA: Food & Drug Administration

Introduction

2020 will go down in history as the year that revealed much about our progress, or perhaps lack thereof, in so many aspects of science, society and culture. Covid-19 has affected every corner of the world. It all began with reports of a new viral illness infecting the residents of Wuhan, the capital city of China's Hubei province. The virus was formally identified in December 2019 as a variant of coronavirus, the family of viruses that had previously caused the outbreaks known as SARS (Severe Acute Respiratory Syndrome) in 2003 and MERS (Middle East Respiratory Syndrome) in 2012, and it was then given the official name SARS-CoV-2 [1].

As of 9th December 2020, there have been over 67.2 million confirmed cases worldwide with over 1.5 million deaths [2]. However, the true number of infections is estimated to be between 3 and 20 times higher, due to incomplete testing of populations as well as false negative rates [3]. The disease resulting from the virus, now called Covid-19 (a contraction of Coronavirus disease 2019), presents with a spectrum of symptoms ranging from asymptomatic or mild malaise to the most severe symptoms of respiratory failure with acute respiratory distress syndrome. The most common presentation is recognised as the combination of fever, non-productive cough and breathlessness, with anosmia also being relatively common and diarrhoea more rare [4]. Of the diagnosed cases worldwide, around 20% require additional respiratory support, with a similar proportion of these requiring ventilation due to severe acute respiratory distress syndrome (ARDS) [5].

Detection methods include Reverse Transcription Polymerase Chain Reaction (RT-PCR) analysis of oropharyngeal aspirate samples, Computed Tomography (CT) imaging of the chest, blood cell differential count and biochemical parameters (such as lymphopenia) and the combination of clinical features with exposure to infected individuals [4].

Treatment options are largely supportive, including the management of fever, hypoxia and dehydration, according to standard healthcare methods. The disease is thought to have two phases; an initial phase of incubation, prodromal illness and emergence of the symptoms as described in the first week, which is followed in some cases by a hyper-immune response in the second week, which can lead to respiratory failure, multi-organ failure and death [5].

While research into the discovery and development of

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a vaccine began almost immediately, the reality was that the process of taking a novel treatment from lab to bedside would require at least a year, not least of all to ensure sufficient long term safety data. Researchers therefore turned their attention to pre-existing, already approved agents for antiviral and immune modulatory purposes, with many drugs being repurposed under the pretexts of off-label or emergency use authorisations, the most popular of which we shall explore below.

Drugs with Antiviral Activity

Chloroquine, Hydroxychloroquine, Azithromycin & Ivermectin

Chloroquine is a famous antimalarial drug of the quinolone class, discovered almost a century ago. It has been observed to have antimalarial, anti-inflammatory and immune modulatory functions, and along with its safer derivative hydroxychloroquine, it has become ubiquitously used in the treatment of connective tissue and autoimmune diseases [6]. The mechanism of action is purported to be through a combination of alkalinisation of endosomal pH, preventing binding of foreign agents, as well as preventing glycosylation of Angiotensin Converting Enzyme II (ACE-II), which in turn inhibits the ability of virus particles to gain entry into the host cell [6].

Azithromycin is an antibiotic of the macrolide class, commonly used in the treatment of Gram-positive as well as atypical bacterial infections. It has also been demonstrated to have anti-inflammatory and immune-regulatory properties *in vitro* as well as in clinical studies, particularly with respiratory viral infections such as influenza [7].

Prior to its attempted use to treat Covid-19, Chloroquine had shown promising *in vitro* results but failed to show efficacy in both animal and clinical trials when tested against the previous coronaviruses (SARS-CoV [6,8] and MERS-CoV), as well as against HIV (Human Immunodeficiency Virus) and even the Influenza virus [9].

Early on in the emergence of Covid-19, Chinese investigators once again demonstrated the *in vitro* potential of Chloroquine for preventing virus to cell entry, as well as mitigating the infectious effects post-entry [10]. An initial clinical trial with 100 patients in Wuhan suggested reduction in the duration and severity of symptoms and improvement in radiographic findings, although this study was not fully published for peer review [11].

Similar non randomised open label trials were conducted in France, including regimens of hydroxychloroquine in combination with Azithromycin, which were primarily designed to prove safety [12,13]. The largest observational study (n = 1438) comparing the use of hydroxychloroquine alone, or in combination with Azithromycin, showed no statistically significant difference in mortality compared to Covid-19 patients hospitalised in New York receiving the usual standard of care [14].

Randomised controlled trials (RCTs) have similarly failed to show benefit of hydroxychloroquine in both hospitalised confirmed cases, as well as for post-exposure prophylaxis purposes in non-hospitalised patients exposed to Covid-19 [15-18]. This includes the UK based Randomised Evaluation of COVid-19 thERapY (RECOVERY) collaborative group trial, which ran until June 2020, showing no difference in 28 day mortality for hospitalised patients and in fact suggesting increased risk of progress to invasive ventilation or death [18].

Safety concerns have also been raised over the use of hydroxychloroquine with or without azithromycin, particularly cardio-toxic and pro-arrhythmic effects purportedly driven by QT prolongation, which had already been observed prior to the use of these drugs in Covid-19 treatment [19]. In a randomised controlled trial including 504 confirmed Covid-19 patients, the frequency of QT prolongation and liver enzyme derangement was increased in those given hydroxychloroquine alone, as well as in combination with azithromycin [17]. Systematic review of trials has found between 10 and 23% incidence of QT prolongation, with a higher frequency of QT_c prolongation > 500 ms in those treated with the combination of two drugs, including reports of associated ventricular arrhythmias requiring emergency cardioversion [20].

Multiple meta-analyses have now been published, which confirm increased risk of adverse effects and no mortality benefit with the use of hydroxychloroquine for Covid-19 treatment [21,22] and instead a significant increase in mortality when combined with azithromycin [22].

In conclusion, the evidence for the efficacy of hydroxychloroquine alone or in combination is unsubstantiated and in fact may confer additional risk to Covid-19 patients. It is currently widely recommended that all patients enrolling on a trial including hydroxychloroquine should have their QT_c interval monitored during treatment, and prior consideration of the risk to benefit profile should be taken for those at increased risk of cardio-toxic effects [23].

Ivermectin is a drug licensed as an anti-parasitic medication, which has also been observed to have antibacterial, antiviral and anti-neoplastic effects [24,25]. *In vitro* studies showed its effectiveness in inhibition of SARS-CoV-2 [26], signalling its potential as a treatment. Pilot observational studies have been promising both for mortality benefit and symptom improvement [27,28], and several RCTs are underway to evaluate this further.

The antiviral agents: Remdesivir, Favipiravir, Lopinavir/Ritonavir & Interferon Beta-1a

Several antiviral agents, all already in existence at the start of the Coronavirus pandemic, have been trialled in an attempt to show efficacy in combating Covid-19.

Remdesivir has probably received the most press due to its patenting and promotion by the American pharmaceutical company Gilead Sciences. It is a broad spectrum antiviral, which has consistently shown efficacy both in *in vitro* and animal models, demonstrating inhibition of SARS-CoV-1 and MERS-CoV [29]. It is an adenosine analogue that is metabolised intracellularly to an analogue of Adenosine Tri-phosphate (ATP), which then serves to compete with natural ATP in the RNA polymerase chain reaction, thereby interrupting

viral replication [29,30].

Remdesivir had been considered as a potential antiviral treatment for Ebola virus, which caused its own transcontinental pandemic in 2018 and 2019. However, it failed to demonstrate significant positive outcomes in the PALM (Pamoja Tulinde Miasha) trial, an RCT involving 681 Ebola patients; in fact it actually showed a significantly worse mortality rate compared to the antibody treatment arm [31].

Once again, Remdesivir showed promise *in vitro* and in animal models for effective SARS-CoV-2 inhibition [10,32], and RCTs got underway. The first of these, conducted by Chinese investigators, found no significant difference versus placebo in Time to Recovery (TTR), viral load or mortality (n = 236) [33].

In April 2020, two sets of trial results were announced. The Adaptive COVID-19 Treatment trial (ACTT) which enrolled 1062 patients across multiple international centres (US, Europe and Asia), showed a 31% improvement in median recovery time compared to placebo (10 days versus 15 days, $p < 0.001$). However, no significant mortality benefit was found [34]. The manufacturer of Remdesivir, Gilead Sciences announced the results of their funded RCT, the SIMPLE trial, purporting to show no added safety concerns from the use of 5 day or 10 day courses of Remdesivir in addition to the standard of care (n = 397). However, no significant difference in TTR or mortality was found between the two treatment course lengths, although the frequency of side effects in the 5 day course arm was reduced. This study was limited by the absence of a placebo control arm [35]. Nonetheless Remdesivir (now under the trade name Veklury), as of 22nd October 2020, has gained full approval in the US to treat Covid-19 [36].

Similarly, the antivirals Favipiravir, Lopinavir and Ritonavir used both individually and in combination also showed initial promise with case reports of success in treating Covid-19 [37]. Lopinavir and Ritonavir is a well- known combination for anti-retroviral treatment in HIV, and had previously been used in the SARS outbreak of 2003 [38]. Multiple small RCTs were conducted, the largest of which (n = 199) showed no statistically significant benefit in mortality, viral load or TTR. It is to be noted however, that this was a cohort of patients with severe Covid-19 symptoms requiring supplemental oxygenation [39]. The UK's RECOVERY group also found a negative result in patients randomised to the Lopinavir/Ritonavir combination versus usual standard of care, with no significant difference in 28 day mortality, median time to discharge from hospital, and no difference in proportion progressing to mechanical ventilation [40].

Most damning of all was the recent publication of the World Health Organisation's SOLIDARITY study on 15th October 2020. This was an open-label international trial investigating Remdesivir, Hydroxychloroquine, Lopinavir/Ritonavir and Interferon-beta 1a, as four separate treatment arms versus placebo controls. It involved the randomisation of 11266 hospitalised patients (2750 of which were randomised to Remdesivir) in 405 hospitals across 30 countries. No statistically significant benefit for mortality, TTR or severity of illness was found with any of these treatments [41]. Gilead sciences claimed a lack of robustness in the WHO data and analysis, which is interesting given the large numbers of patients involved, although they argued that this would increase the confounding factors from variable inclusion criteria, varying international standards of care and severity of illness of the participants [42].

Like the other agents investigated in the WHO SOLIDARITY study, Interferon-beta 1a was repurposed from its licensed indications for viral hepatitis and for multiple sclerosis. It is a recombinant human Type I interferon (naturally occurring signalling proteins known to be part of the innate antiviral immune response) and showed *in vitro* promise at clearing viral loads by inhibiting viral replication [43]. Multiple trials are ongoing, but the WHO data included 1412 patients treated with Interferon only versus standard of care, finding no significant difference on 28 day mortality [41].

Immunomodulatory Therapies, Drugs and Targets

The disease course of Covid-19 is thought to involve two phases: An initial phase of viral activity represented by the emergence of the classically described symptoms, followed by a second hyper-inflammatory phase a week or two later. It is this cytokine storm that is believed to be primarily responsible for the severe deterioration in those that develop Acute Respiratory Distress Syndrome (ARDS), which can result in a downward spiral towards multi-organ failure and death [5,44]. Three major strategies have been identified and trialled in the combat of this second phase. Firstly, use of the 'broad spectrum' immunomodulatory effects of well-established glucocorticoid drugs, such as prednisolone and dexamethasone. Secondly, there has been investigation into drugs directly targeting and inhibiting cytokines, including Granulocyte macrophage Colony Stimulating Factor (GM-CSF) and Interleukin 6 (IL-6). Thirdly, there have also been forays into treatment using plasma obtained from patients who have successfully recovered from Covid-19.

Glucocorticosteroids

Initial anecdotal evidence and small scale trials showed improved outcomes in Covid-19 patients treated with methylprednisolone [45], and in China there has been recommendation for the use of steroids in severe cases [46]. However, as the mechanism of action of glucocorticoids is incompletely understood, there were also widespread concerns over the use of immunosuppressant drugs in severe infective states [47]. However, with the hypothesis that these drugs could mitigate inflammation of the lung parenchyma and thereby lower the risk of progression to respiratory failure, the RECOVERY collaborative group trial got underway. This was an open label RCT with a total of 2104 hospitalised patients randomised to dexamethasone treatment in addition to the usual standard of care, the results from whom were compared to the usual care control group of 4321 patients. A statistically significant decrease in overall 28 day mortality rate was found in the dexamethasone treatment group (hazard ratio 0.83, $p < 0.001$), and this decrease in mortality was even more pronounced in the sub-analysis of patients that required me-

chanical ventilation (hazard ratio 0.64, n = 1007), although no significant difference was found in those patients who did not require supplemental oxygen [48].

A pooled meta-analysis of seven RCTs also confirmed the benefit of administration of systemic corticosteroids, which was associated with lower 28 day all-cause mortality compared with usual care or placebo [49].

On the basis of these results, dexamethasone is now a recommendation for hospitalised patients that require supplemental oxygenation or ventilation, as was announced by the UK Chief Medical Officer in a Central Alert Message on 16th June 2020 [50].

The Cytokine storm: Treatment targets

Immune cell-mediated lung damage has been theorised as a major contributor to the severity of Covid-19. Serum levels of IL-6 were found to be almost ten times higher in severe Covid-19 cases and associated with raised viral loads [51]. As this is only a statistical correlation, it is not clear whether the rise in IL-6 is a cause or effect of the severity of Covid-19 lung infection.

Two anti-IL-6 therapies, Tocilizumab and Sarilumab, have undergone recent trials in treating Covid-19. They are both humanised monoclonal antibodies and were already previously approved for treating autoimmune arthritides and for Chimeric Antigen Receptor T cell (CAR-T cell) therapy in cancer. An initial cohort study in China showed a reduction in fever and oxygen requirement in 21 patients with severe Covid-19 treated with Tocilizumab, although this result had no control group for comparison [52]. A retrospective case control cohort study in Italy in June 2020 compared 544 severe Covid-19 patients, of which 179 patients received Tocilizumab, and showed a significant risk reduction in the composite endpoint of death or mechanical ventilation (hazard ratio 0.60, p = 0.003) [53].

RCTs failed to reproduce such promise, however. Sarilumab's CORIMUNO trial was suspended due to futility, and the industry-sponsored COVACTA trial for Tocilizumab failed to show significant outcomes in any of its primary and secondary endpoints [54]. Indeed, there had already been reservations over the immune-suppressant effects of this class of drugs, as evidenced by their predisposition to secondary infections as seen in long term use with autoimmune conditions and cancer therapies. However, the wide inclusion criteria in the COVACTA trial resulted in a wide range of mild to severe Covid-19 cases in the study, which could confound the result. Multiple cohort studies and clinical trials have suggested that the early combination of Tocilizumab and steroids may confer additional benefit in severe Covid-19 cases [55,56]. Since dexamethasone has now become part of the standard of care, the UK RECOVERY group continues to trial Tocilizumab in severe Covid-19 cases, having already randomised over 850 patients (almost double those enrolled in COVACTA). This will help to shed further light on whether any benefits can be derived from Tocilizumab in combination with dexamethasone in Covid-19 infection [54].

Convalescent Plasma transfusion

Convalescent plasma, obtained from recently recovered patients, had been shown to improve clinical outcomes and reduce mortality in the previous SARS and MERS epidemics [57,58]. Initial case series from China seemed to reproduce this effect in Covid-19 patients, showing clinical improvement, clearing of viral load and reversal of ARDS in four out of five patients [59]. However, subsequent RCTs both in Wuhan, China for severe and life- threatening Covid-19 infection and in India for moderate infections failed to show improvement in mortality or TTR [60,61]. Interestingly, viral load clearance occurred much more quickly in the convalescent plasma treatment group versus standard care control group (87.2% vs. 37.5%, p < 0.001) [61].

Despite these negative results, it is felt that identifying specific immunoglobulins/antibodies from convalescent plasma may hold part of the key to future therapies, including the development of the eventual vaccine [62]. Examples of monoclonal antibodies identified from convalescent plasma include LY-CoV555, which showed promising interim results in a phase 2 trial of 452 patients diagnosed with mild to moderate Covid-19. In patients receiving 2800 mg of LY-CoV555, the viral load reduced by a factor of 3.4 vs. placebo (n = 107, p = 0.02). However, this will require further recruitment and analysis, as the significant difference seen at the 2800 mg dose was lost with a 7000 mg dose, which is counter-intuitive [63]. Despite this, on 9th November 2020 the US Food and Drug Administration (FDA) authorised its use for mild to moderate cases of Covid-19 infection not requiring hospitalisation, with the new drug christened 'Bamlanivimab' [64].

Another promising example is REGN-COV2, a combination of two human monoclonal antibodies identified from convalescent plasma, which targets the spike glycoprotein of the SARS-CoV2 virus. *In vivo* study in Rhesus macaques and golden hamsters showed potential for both prophylaxis as well as treatment of Covid-19, with clearing of viral loads and amelioration of lung pathology [65]. The developers of this cocktail, Regeneron Pharmaceuticals, recently announced interim results from its ongoing phase 2/3 trial of 275 recently diagnosed mild to moderate (non-hospitalised) Covid-19 patients randomised to either one of two doses of REGN-COV2 or placebo. Their results show highly significant reductions in viral load versus placebo with both high and low doses of REGN-COV2, although statistical significance was not achieved for the numerically lower median time to symptom alleviation [66]. This study is ongoing and has not been published fully for peer review; however due to promising findings the UK RECOVERY collaborative research group has commenced phase 3 trials to establish the benefits of REGN-COV2 in hospitalised Covid-19 patients [67].

In Hospital Considerations: Supportive Measures & Therapies

Coagulopathy & thromboembolism

Following on from the theory of immune-mediated hyper-inflammatory state contributing to severe Covid-19 infec-

tion, it has been widely suggested that hypercoagulability is at least partially responsible for ARDS in these cases. A combination of SARS-CoV2's affinity for pulmonary ACE-II receptors, diffuse interstitial and alveolar damage, the activation of macrophages and cytokines arriving from the pulmonary vascular endothelium, as well as profound hypoxia leading to increased plasma viscosity, is purported to predispose to coagulation in the pulmonary microvasculature in a similar manner to that seen in disseminated intravascular coagulation (DIC) in overwhelming sepsis [68]. Initial case reports emerged describing a DIC-like picture in severe Covid-19 infection, and there have also been case reports of systemic thromboembolism [69,70]. This hypercoagulable state is thought to cause the highest risk in the second week of the infection course, as illustrated by a significant rise in inflammatory markers (C reactive protein), D-dimer and Fibrinogen [71].

A retrospective analysis of 449 patients in a Wuhan hospital showed an apparent mortality benefit from the use of low molecular weight heparin (LMWH) for 7 days in the most severe cases of Covid-19 infection [72]. Further analysis of this data revealed that the mortality benefit was mostly seen in those patients receiving heparin who had a raised D-dimer [73].

It has already been established from previous meta-analysis of RCTs in ARDS patients that administration of LMWH can reduce the risk of mortality (48% 7 day mortality risk reduction, 37% 28 day mortality reduction) [74]. Therefore, although prospective RCTs are lacking for the use of anticoagulation in Covid-19, there has been a widespread recommendation for evaluating the thromboembolic risk of all hospitalised Covid-19 patients [68]. Algorithms for calculating the risk and determining the need for anticoagulation have been proposed by the European Society of Cardiology, who have suggested a heparin infusion for intensive care patients and a subcutaneous regimen of 1 mg/kg twice daily for non-high dependency patients [75].

Oxygenation, ventilation and proning

The most severe presentation of Covid-19 infection is with respiratory failure and ARDS, which is associated with a high risk of mortality [5]. Management of the airway of critically ill patients is challenging, and the increased risk of viral transmission to healthcare workers (HCWs) is now well documented during aerosol generating procedures (AGPs) [76]. Early on in the pandemic, some intensivists argued for early intubation and ventilation for Covid-19 patients even in cases with mild respiratory failure, suggesting that progressively vigorous inspiratory effort was the cause of lung injury [77]. However, with time it was recognised that despite meeting clinical criteria for ARDS, many Covid-19 patients had a mismatch between the degree of measured hypoxia and their lung compliance, with profound hypoxaemia in the presence of little respiratory distress [78]. Although mechanical ventilation is a life-saving intervention, it does not directly help the body to heal lung injury and in essence 'buys time' for the infected patient to develop an adequate immune response [76,79]. However, it would be extremely difficult to design a RCT in this severely unwell cohort of patients, not least of all due to the inability to blind intervention versus controls and the ethical unsoundness of such a venture.

Nonetheless, non-invasive ventilation treatment options are being compared in the UK RECOVERY (RECOVERY-RS) group trial, with 200 patients randomised so far as of 12th October 2020 to help evaluate the effectiveness of Continuous Positive Airway Pressure (CPAP) and High Flow Nasal Oxygen (HFNO) versus standard care for Covid-19 patients with respiratory failure not requiring imminent intubation. This study is aiming to recruit 4000 patients into the 3 arms and is anticipated to complete in April 2021 [80].

Conscious proning has emerged as another possible therapeutic option in hospitalised patients not requiring ventilation. Prone positioning has been proven in RCTs and meta-analysis over the past two decades to be beneficial in improving oxygenation in mechanically ventilated ARDS patients, and rotational positioning has been adopted by intensive care units worldwide [81,82]. Multiple case series of conscious proning in moderate cases of hospitalised Covid-19 patients have now been published over the course of the pandemic, claiming to show improvement in hypoxia and potentially averting the need for intubation [83,84]. However, a rapid review of these studies concluded that the evidence base was hampered by a lack of any published RCTs, and that the results from ongoing RCTs will be needed to help decide if this is indeed a worthwhile intervention [85].

Preventive Therapies and the Vaccine

While vaccine development continued, the WHO recommended measures for the prevention of Covid-19 infection consisted of the strategies of social distancing, wearing face masks, frequent hand washing and isolation/quarantine measures for those infected or exposed to infected individuals [86]. In hospital settings, this extended to include guidelines for the use of personal protective equipment (PPE), with the use of the Filtering Face-Piece (FFP) class 2 and 3 masks conferring 95% and 99% fine particle filtration efficacy respectively [87].

December 2020 has finally seen the announcement and approval of a novel messenger RNA (mRNA) based vaccine purported to have 95% efficacy in preventing Covid-19 infection, developed by the pharmaceutical companies Pfizer and BioNTech in collaboration. Despite no Phase III trial results being published in peer- reviewed journals as of 10th Dec 2020, the UK Medicines and Health Regulatory Agency, an independent body, approved this vaccine on 2nd Dec, based on trial results made available to them prior to publication. This was unprecedented as the UK would normally await approval by the European Medicines Agency (EMA) prior to authorising the distribution of a new drug. The UK government made legislative changes in October 2020 allowing emergency use authorisation for such a scenario. The MHRA reported no safety concerns and were satisfied with the efficacy results [88]. The UK National Health Service began offering the vaccine to adults aged over 80 years of age on 8th December 2020 [88]. The Moderna pharmaceuticals vaccine is also mRNA-based and is yet to have results published or achieve approval, de-

spite reportedly similar positive interim results.

The AstraZeneca/Oxford ChAdOx1 nCoV-19 vaccine is a replication-deficient adenovirus modified to express the SARS-Cov-2 structural surface glycoprotein. Interim results from the first 11,636 trial participants have just been published, showing up to 90% efficacy (p = 0.01) depending on the dose regimen, with no significant safety concerns [89]. The trial is ongoing with a total of 23,848 participants enrolled by November 2020, and the scientific community awaits the full results with interest; as a 'traditional' vaccine it is likely to be the most cost- effective and widely used should it gain approval.

Conclusion

It is now clear that the treatment of Covid-19 requires a multi-faceted approach, considering both the severity of infection, the two phases of its clinical syndrome and the mechanisms of organ injury. The only drug class that has shown proven benefit so far is ironically one of the oldest; glucocorticoids, in particular Dexamethasone, have humbled the medical profession yet again. And an even older medicine- heparin- is also rapidly becoming considered an essential part of the treatment of severe Covid-19. However, as we are now deep into the so-called 'second wave', much vital research is ongoing. There is promise in the initial results seen from trials of human monoclonal antibodies conferring passive immunity, but it remains to be seen if these will actually prove to be the much-needed remedy or in the end fall by the wayside along with so many of the other trialled treatments. Nonetheless, with the approval of multiple vaccines around the corner, a glimmer of hope has emerged that we are finally on the cusp of conquering this disease (Table 1).

Conflicts of Interest

None.

Table 1: Summary table of trialled therapies for Covid-19.

Drug/treatment	Class/Mechanism of action	Results of Covid-19 trials
Drugs with antiviral activity		
Chloroquine/ Hydroxychloroquine	-Quinolone class (antimalarial) -Alkalinisation of endosomes & inhibition of ACE-II glycosylation, preventing virus binding & cell entry	RECOVERY trial- no significant difference in mortality or TTR. Confirmed with multiple meta-analyses Aug 2020 [21,22]
Azithromycin	-Macrolide bacteriostatic antibiotic -Inhibits mRNA translation on bacterial ribosome; theorised to have similar effect on virus	Increased risk of adverse effects and mortality in combination with hydroxychloroquine (meta-analysis of 7 studies) RR1.27, 95% CI 1.04-1.54 [22]
Ivermectin	-Antiparasitic macrocyclic lactone -Cellular hyperpolarisation via binding glutamate-gated chloride channel receptor (GluClR) causing cell paralysis/death	*In Vitro* effectiveness against SARS-CoV-2; cohort study meta-analysis suggests mortality and TTR benefits [27,28]. RCTs awaited.
Remdesivir	-Prodrug- active metabolite ATP analogue -Inhibits RNA-dependent RNA polymerase, preventing viral replication	31% Improvement in TTR, no effect on mortality in ACTT trial (p < 0.001) [35]. SIMPLE trial showed no additional safety concerns (not placebo controlled) [36]. Approved by US FDA Oct 2020.
Favipiravir	-Prodrug- active metabolite inhibits RNA-dependent RNA polymerase -Prevents viral replication	WHO SOLIDARITY Study: No significant benefit in mortality, TTR or illness severity [42].
Lopinavir/ Ritonavir	-Anti-retroviral drug combination (HIV protease inhibitors) -Bind viral protease, preventing antigen production	Largest RCT (n = 199) showed no benefit in TTR, mortality or viral load clearance [40]. WHO SOLIDARITY Study: No significant benefit in mortality, TTR or illness severity [42].
Drugs with immunomodulatory functions		
Interferon Beta-1a	-Recombinant human interferon (cytokine); licensed for Multiple sclerosis -Reduces inflammation, inhibits production of T helper cells	WHO SOLIDARITY Study: No significant benefit in mortality, TTR or illness severity [42]. RCTs ongoing trialling inhaled regimen.
Glucocorticoids	-Anti-inflammatory, pleotropic effects and usage -Bind glucocorticoid receptors, stimulating anti-inflammatory protein production	RECOVERY trial (n = 2104 vs. 4321 usual care): Decreased 28-day mortality HR0.83, p < 0.001 [49]. Confirmed with Pooled meta-analysis of 7 RCTs [50].

Tocilizumab	-Humanised monoclonal antibody (anti-IL6 cytokine receptor); licensed for Rheumatoid arthritis -Suppression of pro-inflammatory interleukin 6	COVACTA trial- no significant difference in mortality, TTR [55]. Cohort studies suggest benefit in combination with steroids [56,57]. RECOVERY trial ongoing.
Sarilumab	- Humanised monoclonal antibody (anti-IL6 cytokine receptor); licensed for Rheumatoid arthritis -Suppression of pro-inflammatory interleukin 6	CORIMUNO trial halted in Sep 2020 due to lack of efficacy [55].
Convalescent plasma	-Antibodies from the plasma of Covid-19-recovered individuals -Likely to confer passive immunity only	Two RCTs (China, India) failed to show mortality or TTR benefit despite significantly quicker viral load clearance [61,62].
Bamlanivimab	-Monoclonal antibody identified from convalescent plasma -Likely to confer passive immunity only	Interim RCT results show significant viral load reduction with lower dose (2800 mg) not seen with 7000 mg dose [64]. US FDA approval in Nov 2020 for non-hospitalised Covid-19 cases (prior to full publication of trial results) [65].
REGN-COV2	-Combination of two monoclonal antibodies identified from convalescent plasma - Likely to confer passive immunity only	Interim RCT results show significant viral load reduction but no difference in TTR in non- hospitalised Covid-19 patients [67]. RECOVERY trial ongoing for hospitalised patients [68].
Supportive measures		
Anticoagulation	-Heparin and derivatives -To treat hypercoagulable pro-inflammatory state	Evidence base from historical (pre-Covid-19 era) meta-analysis of RCTs in ARDS patients showing 48% 7-day and 37% 28-day reduction in mortality [75]. Retrospective analyses of Covid-19 patients in China show apparent mortality benefit of 7 days anticoagulation with LMWH [73,74].
Non-invasive ventilation, conscious proning	-Positive/bi-level pressure mask ventilation to aid oxygenation in hypoxic states -Proning (alternating supine and prone positioning during ventilation to allow aeration of entire lung)	RECOVERY-RS trial ongoing to evaluate HFNO vs. CPAP [81]. Case series show conscious proning in moderate cases of Covid-19 shown improves hypoxia and decreases risk of progression to intubation [84,85].
Invasive ventilation	-Mechanical ventilation after endotracheal intubation used in cases of severe hypoxia and poor respiratory reserve	Mechanical ventilation known to be lifesaving in ARDS. Difficult to ethically design RCT.
The Vaccines		
Pfizer/BioNTech	-messenger RNA coding for SARS-CoV-2 surface spike glycoprotein -Stimulates production of antibodies to the resulting antigen without viral infection	Approved by UK MHRA and US FDA in Dec 2020 on basis of results made available prior to peer-reviewed publication [89].
Moderna	-messenger RNA coding for SARS-CoV-2 surface spike glycoprotein -Stimulates production of antibodies to the resulting antigen without viral infection	Awaiting publication of full results; interim results announced claiming 95% efficacy
Oxford/AstraZeneca (ChAdOx1 nCOV-19)	-Replication deficient adenovirus modified to express SARS-CoV-2 surface spike glycoprotein	Interim results of 11,636 trial participants showing up to 90% efficacy at low dose regimen with no significant safety concerns [90]. Full results awaited.

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