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CHAPTER

Novel treatments and trials in COVID-19

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Coronavirus disease 2019 (COVID-19), the disease arising from the beta coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has presented a major challenge to health-care systems and societies across the world.[1] Although previous highly pathogenic coronaviruses have emerged, namely severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV), neither had the spread nor the persistence to result in large clinical trials of drug therapy. Much of our therapeutic knowledge in these viruses was therefore informed by inference from observational, in vitro, and experimental model studies. As a result when SARS-CoV-2 emerged, with a noted high morbidity and mortality,[2] initial therapeutic drug treatment was often empiric.[2] There are currently over 4400 trials concerning COVID-19 registered on the World Health Organization international clinical trials registry, and while not all these are interventional therapeutic trials, this illustrates the desire of the international clinical-scientific community to develop systematic and evidence-based approaches for the management of this major threat.

This chapter discusses the broad strategies of therapeutic pharmacological approaches suggested, namely antiviral therapy, antiinflammatories, and immunomodulatory. Nonpharmacological approaches are also to be discussed. Then, it reviews the approaches to trials and trial design, the development and use of core outcome sets, and regulation of trials in pandemic settings. It reviews the publication and preprint availability of completed trials before discussing the ethics of empiric treatment outside the context of trials.

Therapeutic approaches

The three broad pharmacological approaches to COVID-19 are antiviral therapy, antiinflammatory, and immunomodulatory.

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Antivirals

COVID-19 arises from an interaction between the virus and the host immune response. Antiviral therapies have proven benefits in a range of viral infections, from human immunodeficiency virus (HIV) to hepatitis B and C and the Herpesviridae such as herpes simplex and cytomegalovirus.[3] The history of antiviral efficacy in respiratory viral illness is less positive, and while licensed treatments exist for influenza in the form of oseltamivir, its effect on illness course and mitigation of critical progression remain uncertain.[4] Evidence of effective antiviral therapy in SARS-CoV-1 and MERS-CoV-induced SARS was limited, with much of it coming from either animal models of disease or in vitro studies and no therapies proven in clinical trials.[5]

RNA-dependent RNA polymerase inhibitors

Originally developed for the treatment of the viral hemorrhagic fever Ebola arising from the filovirus *Zaire ebolavirus*, remdesivir is an RNA-dependent viral RNA polymerase inhibitor with broad in vitro activity against multiple families of viruses including Filoviridae, Pneumoviridae, and Orthocoronaviridae, the family to which the beta coronaviruses belong.[6] It had demonstrated efficacy in a mouse model of SARS-CoV-1 infection.[6] Recent trials in COVID-19 showed divergent outcomes, a study indicating faster resolution in hospitalized patients needing oxygen but not among those with more severe respiratory failure. However, the large SOLIDARITY trial did not demonstrate benefit.[7] Despite the negative results from the SOLIDARITY trial, Remdesivir retains emergency use authorization in a number of jurisdictions.

Favipiravir, which also targets RNA-dependent RNA polymerase, is being tested in number of ongoing trials, although completed studies to date are small, and efficacy remains to be proven.[8]

Protease inhibitors

Protease inhibitors are central to the management of HIV and also target proteases in Orthocoronaviridae.[5] In a marmoset model of MERS-CoV infection, the combination of lopinavir/ritonavir improved disease severity and viral clearance.[9] An early phase II randomized controlled trial comparing lopinavir/ritonavir with combination therapy, ribavirin and interferon beta suggested that combination therapy was superior to lopinavir/ritonavir alone.[10] However the lopinavir/ritonavir arms of the Randomized Evaluation of COVID-19 Therapy (RECOVERY) and SOLIDARITY trials indicate that it was not superior to placebo.[7,10,11]

Antimalarials

Chloroquine, and its derivative hydroxychloroquine, have well-established antimalarial activity. They are also commonly used in vitro for their effects on endosomal acidification and demonstrated in vitro activity against MERS-CoV.[12,13] Despite

widespread adoption, concerns have been raised about the effect on cardiovascular mortality possibly linked to prolonged QT interval.[14] However, although neither the RECOVERY nor SOLIDARITY trials demonstrated any benefit of hydroxychloroquine,[7,15] they also did not indicate any excess of cardiovascular events attributed to this drug.

Antibiotics

Some antibacterial drugs also have antiviral properties, including azithromycin and teicoplanin.[16,17] Azithromycin has attracted particular attention as it may synergize with hydroxychloroquine, although the retrospective survey of patients reporting this has attracted notes of concern.[18,19]. The RECOVERY study azithromycin arm did not find any benefit, although neither did it find evidence of increased cardiac dysrhythmias.[20]

Convalescent plasma and immunoglobulins

Convalescent plasma, as a form of passive immunity, has a long history of use in viral illness, although large-scale randomized trials are lacking.[21] Convalescent plasma is a heterogenous treatment with varying titer levels, and although early use of high-titer plasma was associated with reduced disease progression in a small study of older adults,[22] the RECOVERY trial convalescent plasma arm was closed following a neutral result at interim analysis (formal publication is awaited). Although nonspecific intravenous immunoglobulin G is often used for patients with immunoglobulin G deficiencies for the prevention and treatment of infectious diseases, it also has immunosuppressive capabilities which are utilized in inflammatory diseases, specific evidence for its use in COVID-19 is lacking.

Antiinflammatories

Corticosteroids

Corticosteroids have long been used for ameliorating harmful inflammatory responses in infectious diseases, with proven roles in meningococcal septicemia and improvements in hemodynamics, and possibly mortality in septic shock.[23,24] Observational data suggested that their use may be harmful in MERS and SARS as well as pandemic influenza.[5,25] However, in COVID-19, several studies have demonstrated benefit among patients on mechanical ventilation or receiving oxygen, but not among the less severely unwell.[26]

Cytokine and complement blockade

Early observations that COVID-19 was associated with raised levels of cytokines, in common with other severe respiratory infections, have prompted interest in blockading proinflammatory cytokines. [27,28] Interleukin (IL)-6, for which there are several licensed biologic therapies, has been the dominant focus of therapeutic

studies, with recent publications indicating efficacy in moderate to severe disease.[29] Additional therapies listed as being trialed on clinicaltrials.gov include blockade of complement C5 with ravulizumab, blockade of IL-1 with anakinra, tumor necrosis factor with infliximab, and colchicine as a broad-spectrum antiinflammatory, none of these trials have yet reported. An alternative approach targeting the intracellular signaling pathways such as the JAK-STAT pathway is also under investigation.

Immunomodulatory therapies

Although COVID-19, and indeed other severe infections, is associated with high levels of cytokinemia, there is evidence of secondary immune failure reflected in the high rate of secondary infections and impaired immune cells responses in the most severely unwell.[27,30] This has led to a number of ongoing trials of immunomodulatory drugs, including recombinant IL-7, granulocyte-macrophage colony-stimulating factor (GM-CSF), and blockade of the negative co-stimulatory molecule programmed cell death protein 1 with nivolumab. Interferon beta-1 has been trialed, usually in combination with protease inhibitors, following its efficacy in the marmoset model of MERS[10]; however, studies have not so far shown benefit.[7]

Mesenchymal stem cells (MSCs) have been trialed in acute respiratory distress syndrome (ARDS), and a small nonrandomized study was recently published in patients with COVID-19.[31,32] The mechanisms by which MSCs may improve outcomes are pluripotent but may include GM-CSF secretion, microvesicle release, enhanced fluid clearance, and pathogen phagocytosis.[33] The results of definitive treatment in COVID-19 are awaited.

Nonpharmacological interventions

For critically ill patients, many of the most well-proven interventions are nonpharmacological. Often these interventions seek to avoid harm caused by the organ support required for those with multiple organ failure and include low tidal ventilation and negative fluid balance in ARDS, restrictive transfusion thresholds, and late implementation of renal replacement therapy.[6,34–37] For patients with COVID-19 who meet the criteria for these previous trials, such interventions reflect best evidence-based supportive care. Proning of mechanically ventilated patients with ARDS is proven to improve mortality and demonstrates efficacy in COVID-19 as much as other causes of ARDS. Whether a similar approach is tolerable and effective in patients who do not require mechanical ventilation and sedation is being tested in several ongoing clinical trials, as are strategies for improving oxygenation and gas exchange such as noninvasive (mask) ventilation, high-flow nasal oxygen cannulae, and application of continuous positive airway pressure.

Timing of interventions

COVID-19 is a disease which starts with viral infection and progresses to an immunopathological state which may persist after the virus has been cleared and demonstrate discordance between presence of viral particles, inflammatory cell infiltration, and clinically apparent organ function.[38] It is likely that treatments that are effective at one stage of the disease may not be so effective at other stages. As an example, dexamethasone appears to be effective more than 7 days after the onset of symptoms, but not in the first 7 days while the apparent lack of efficacy of remdesivir among ventilated patients may reflect the relative late point at which ARDS develops relative to onset of symptoms.[26,27,39] While it remains speculative, it is possible that these differences reflect early viral proliferation that might be worsened by immunosuppressive corticosteroids, with later immunopathology that benefits.

Trial design

Clinical trials for novel therapeutics usually work their way through the widely adopted process of preclinical efficacy in cellular and animal models and toxicity testing before entering human studies. These then build through the phases from safety and dose finding (phase 1) usually undertaken in healthy volunteers, before early and midphase studies in the target patient population (phase 2) before entering the definitive phase 3 trials where clinical effectiveness in determining the outcomes of interest is tested. To get from a candidate molecule to licensed pharmaceutical can often take 10–15 years, and in a pandemic with urgent need for novel therapies, this timescale is clearly impractical. As a result, a number of processes have been adopted to try to reduce the time from discovery to implementation. As the proliferation of trials concerning COVID-19 has continued, repeated warnings have been issued about trial quality and rigor.[40]

Repurposing existing medication

As the review of therapeutic approaches above demonstrates, the dominant approach to treatment of COVID-19 is to repurpose existing pharmaceutical agents which are already licensed for alternative indications. Even where a drug has no existing license such as in the case of remdesivir, they were agents developed for other viral infections with at least preliminary use in humans. While this runs against the trend toward targeted drug design, it did allow early rapid implementation of phase 3 clinical trials.

Compassionate use and observational registry-based studies

When novel pathogens emerge, the lack of previous biological and clinical experience with them can make clinical decision making difficult. The imperative to try to treat and cure patients can then lead to empiric therapy, based on strategies derived

from similar diseases. During the COVID-19 pandemic, this was challenging as neither of the related diseases (MERS or SARS) has a strong underpinning of evidence.[5] While the relationship between a single practitioner's individual therapeutic decisions and outcomes can never be determined with certainty, large-scale observational studies can allow detection of potential treatment effects but are at risk of significant bias. As noted in the reviewed approaches above, several drugs that had biologically plausible effects did not prove beneficial in phase 3 trials, and this should sound a note of caution over the use of empiric therapy out-with the context of a clinical trial.

Randomized controlled trials

Randomized controlled trials are the gold standard of clinical therapeutic investigations. While their use in the heterogenous syndromes that make up the dominant workload in critical care has been questioned,[41] for well-defined disease states, they remain our strongest defense against ineffective or dangerous interventions. There is an extensive literature on the design, conduct, and evaluation of randomized trials,[42] which are not reviewed in depth here, but key markers of trial quality have been identified and should be looked for when reviewing results. These refer not only to specific trial design features (randomization, blinding, handling of dropout, loss to follow-up, a priori power calculations, and recruitment to power targets) but also to trial conduct, which should include registration, publication of trial protocol and statistical analysis plan prior to completion, and commitment to data availability for post hoc analysis. Where trials are sponsored by commercial enterprises that may benefit financially from the results, independence of the trial delivery, and analysis team from that commercial entity should be looked for. Various investigator groups have demonstrated that it is possible to deliver high-quality large randomized trials despite the clinical and social pressures induced by the COVID-19 pandemic.

Complex innovative design

The desire to rapidly identify effective treatments for COVID-19 has led to more widespread adoption of more complex and innovative trial designs.[43] Complex innovative design (CID) covers a range of trial designs, including umbrella, multiarm, and adaptive approaches.[43] During the COVID-19 pandemic, platform trials, which use combinations of multiarm and adaptive approaches underpinned by a common protocol, have found favor. Notable examples of such approaches include the RECOVERY, Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP-CAP),[5] and Solidarity platforms, which have evaluated a range of interventions.[44–46] Through the use of common control groups, against which each of the interventions can be assessed, and the structured addition of intervention arms, these platforms can deliver rapid but

robustly evaluated results. REMAP-CAP is particularly interesting as it was a pre-existing adaptive study that was repurposed to include COVID-19. Adaptive trials allow for the conduct of the trial to be modified by the results it generates, and to include multiple and sometimes combined treatment arms.[47] This sort of design not only maximizes the efficiency of the study but also allows for examination of interactions between trial interventions.[47] CIDs need considerable thought and planning, and rapid implementation requires the infrastructure to be in place or able to be rapidly implemented. Funding foresight and investment in "potential trials" that are in place before they are needed are key to ensuring such studies can be successfully deployed.

Regulation of clinical trials

Clinical trials are conducted under the auspices of the national and local regulatory bodies, each of which has its own requirements and procedures. The international committee on harmonization has sought to establish common standards across many of the major regions conducting clinical trials, ensuring that results from one region can be used for regulatory approvals in another. In the context of a rapidly evolving global pandemic, this becomes increasingly important.

Core outcomes

There has been a proliferation of trials in response to COVID-19, however, the wide heterogeneity of outcomes reported and omission of patient-reported outcomes can limit the use of this evidence for informed decision making. Core outcome sets can improve consistency in the reporting of critically important outcomes. Four initiatives have been established for COVID-19, and all have identified mortality and respiratory failure as core outcomes.[48–52] The World Health Organization candidate core outcome measure sets include viral burden, survival, and clinical progression to assess the severity of disease.[48] Recently, the global COVID-19 Core Outcomes Set initiative was launched to establish core outcomes for people with suspected or confirmed COVID-19. Based on a systematic review of outcomes reported, published and registered trials, an international online survey conducted in five languages involving 9289 patients, caregivers, health professionals and members of the general public from 111 countries, and four consensus workshops, five core outcome domains were identified: mortality, respiratory failure, multiorgan failure, shortness of breath, and recovery[51,52] and the core outcome measures arising from these have been published.[53] The implementation of core outcomes in trials in COVID-19 can help to ensure that outcomes of critical importance to all stakeholders are consistently reported in trials to better support informed decision making.

Publication and preprints

COVID-19 has seen an explosion in the use of clinical study and trial preprints, where manuscripts are posted on a publicly available server prior to peer review. The major medical and biological preprint servers, MedRxiv and BioRxiv, currently record 5230 and 1345 COVID-19 manuscripts, respectively. In contrast, MedRxiv records only 2355 manuscripts concerning influenza, a far more long-standing viral threat. The advantage of preprint deposition is that it allows for rapid dissemination of key findings, which during a fast-moving pandemic can help inform clinical decision making. However, as preprints will only have been reviewed within the research team, there is a greater potential for flawed or incomplete results to be released, and readers will have to conduct a higher degree of critical appraisal themselves. However, it also allows for "community peer review," which was perhaps most clearly seen following the release of the dexamethasone arm of the recovery trial.[54] Preprints do not replace formal peer-reviewed publication but should be seen as rapid notification of preliminary results.

Ethics of empiric therapy outside clinical trials

At the core of medical ethics lie the principles of autonomy (allowing the patient to make informed decisions), nonmaleficence (first do not harm), beneficence (serving the best interests of the patient), and justice (ensuring equitable treatment to all patients). While the treatment imperative may seem to demand action, one of the key lessons from the experience of COVID-19 has been of the perils of empiric therapy founded on personal clinical experience and biologically plausible therapies not subjected to clinical testing. These may violate several principles of medical ethics, as patients may come to harm with no potential for benefit, while being denied both the personal and wider societal benefits that may accrue from participation in clinical trials. Patients should be offered the best-proven treatments, including supportive care. Where empirical therapies are considered, these are the most ethically delivered in the context of an appropriately designed and regulated clinical trial. Where this is not possible, consenting patient data should be submitted to case registries.

In conclusion, COVID-19 has presented a major challenge to health-care services as clinicians have urgently sought effective treatments. Reliance of limited experience from previous similar diseases sometimes led to the use of empiric therapies which, when tested in large randomized trials, prove to be ineffective. As it has been possible to deliver high-quality, multicenter, and indeed multinational trials during the pandemic, this approach is likely to improve outcomes for patients with COVID-19.

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