EDITORIAL

How likely are COVID-19 interventions to benefit the sickest patients?

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The coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in more than 4.3 M infections and 297,000 deaths worldwide [1]. It has placed an unprecedented demand on healthcare and overwhelmed the capacity of critical care services in some countries. The manifestations of COVID-19 vary from fever and mild upper respiratory tract symptoms to pneumonia, acute respiratory distress syndrome (ARDS), and multiple organ failure resulting in death [2]. Worsening disease may be driven by increased viral load and hyper-inflammation in addition to increasing age and co-morbidities [2]. Capitalising on this knowledge, several trials are underway testing the efficacy of anti-viral agents, anti-malarial agents, immune modulators, and angiotensin receptor blockers.

Currently, there are no approved treatments for COVID-19, and care is therefore supportive. Some patients have been treated off-label or in compassionate use programs with agents having potential antiviral and/or immunomodulatory actions (Fig. 1) [3]. For now, a few of these agents have been assessed in randomized clinical trials (RCT) but none in RCTs with the quality to assess the balance between benefits and harms [4, 5]. In addition, there are observational studies of the use of remdesivir [6], hydroxychloroquine [7] and convalescent plasma [8] in patients with COVID-19, but they have major methodological flaws. The publication of these results in high impact journals combined with mainstream and social media attention and well-intentioned, but misguided physician enthusiasm, has meant a rapid

uptake of unproven interventions in several countries. Researchers have expressed concerns about the endorsement of such therapies by prominent political leaders and governments [9, 10].

In this background, the key question is if these drugs provide real benefit to patients. The question is particularly important in the critically ill COVID-19 patients because they have more at stake; benefit from the interventions may improve their survival and quality of life—harm may do the opposite.

Indirect evidence from other viral respiratory infections

The development of treatments for viral respiratory infections has been a very challenging process despite decades of research into the viruses and the host response. While remdesivir and hydroxychloroquine may have in vitro effects against SARS-CoV-2 [3], they were not developed for this. The failure of remdesivir in Ebola virus disease [11], for which it was developed, and the modest effects of antivirals in patients with influenza or respiratory syncytial virus makes it less likely that remdesivir or hydroxychloroquine will benefit patients with COVID-19. While the Adaptive COVID-19 Treatment Trial allegedly found shorter time to recovery as compared to placebo in patients with moderate to severe COVID-19 as announced by a press release [12], we need to see the full trial report, including the methodological details, effects on patient-important outcomes and adverse effect, to understand these results. In particular as a fully published similar trial from China found no obvious benefit of remdesivir in these patients [13].

The case may be different for convalescent plasma as this by concept is specific against SARS-CoV-2. Again, data from influenza should dampen our expectations. In a placebo-controlled RCT, the use of anti-influenza hyper-immune intravenous immunoglobulin (hIVIG) provided

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Fig. 1 Potential benefits and harms of interventions used in patients with COVID-19

no overall benefit for adults hospitalised with influenza infection [14]. In that trial, there may have been an interaction in the intervention effect by the type of influenza; those with influenza A may have been harmed from hIVIG while those with influenza B may have benefited. The latter observation shows the complexity and risk of the use of untested interventions in severe viral disease no matter how good the a priori rationale appears.

Indirect evidence from ARDS and sepsis

Similarly, in ARDS and sepsis the development of therapeutic interventions has been challenging. While the case has been built for the use of inhibitors of the 'cytokine storm', which is believed to drive worse outcomes in COVID-19, such strategies have failed in previous trials of various inflammatory modulators. And some of these modulators may have harmed patients [15]. While the

nonspecific anti-inflammatory effects of corticosteroids may offer some benefit in patients with ARDS [16] and appear to benefit those with sepsis [17], most of these patients have bacterial infections and receive appropriate antibiotic therapy. As noted above, there is no effective antiviral agent against SARS-CoV-2. The obvious risk of using steroids in patients with COVID-19 is the suppression of the immune system, which may be the patient's only defense against the virus. In contrast, interferon-beta may stimulate the innate anti-viral response, and interferon-beta-1a was recently tested in non-COVID-19 ARDS because of proposed effects on the vascular leakage [18]. The results of the latter trial were neutral both regarding efficacy and adverse effects, but interferon-beta-1a has multiple registered adverse effects when given for other indications.

Lessons from the use of low-level-evidence interventions in other critically ill patients

Unfortunately, the situation described above is not unique in critical care; many interventions administered to critically ill patients have been based on pathophysiological reasoning of expected benefit with less focus on adverse effects. Thus, many interventions in critical care have been shown to offer no benefit or result in harm when finally tested in RCTs [19]. The risk of harm from interventions may be higher when the adverse reaction appears indistinguishable from the natural history of the disease as it was the case for hydroxyethyl starch and kidney injury in patients with sepsis [20]. Clearly, this risk is also present for patients with COVID-19. While we still have very limited understanding of the pathophysiology, it is obvious that many of these patients develop the severe complications seen in other critically ill patients including brain, circulatory, hepatic and kidney failure and thromboembolic events. It will be very difficult, if not impossible, to determine if these severe complications arise primarily from the disease or from severe adverse reactions to off-label interventions used in patients with COVID-19.

Summing all this up, the net benefit is far from certain for all the therapeutic agents now used off-label or in compassionate use programs against SARS-CoV-2 and COVID-19, and the risk of harm is high. The testing of these interventions in large, multi-center, randomized trials with high internal and external validity, is not only a scientific necessity, but also an ethical and a moral imperative. The setting of an RCT protects the patients through the rigorous monitoring and handling of serious adverse events and helps future patients and society by producing unbiased results on the delicate balance between the benefits and harms.

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Compliance with ethical standards

Conflicts of interest

AP is the Sponsor of the COVID STEROID trial (NCT04348305), which is funded by the Novo Nordisk Foundation and supported by Pfizer Denmark. BK is site investigator for the SOLIDARITY trial for Apollo Hospitals, Chennai and the country PI for the Lessening Organ dysfunction with Vitamin C in Sepsis trial (LOVIT India).

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 24 April 2020 Accepted: 21 May 2020

Published online: 9 June 2020

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