PHARMACOTHERAPY

COVID-19: Important Therapy Considerations and Approaches in this Hour of Need

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We are living in unprecedented times. While we had near-pandemic events in the recent past with SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome), we have never experienced anything like coronavirus (COVID-19), also known as SARS-CoV-2 infection, since the Spanish flu. In contrast to the Spanish flu where medical care was limited, we are equipped better to combat COVID-19, but there is considerable work ahead with many uncertainties. At this critical time, we must come together as one united country and world to stop the spread and provide the best care possible for individuals who contract the virus and develop infection. A number of novel and repurposed therapies agents with activity against SARS-CoV-2 have been identified, and most institutions have developed clinical pathways to operationalize their use in appropriate COVID-19 patients.[1–3] However, optimal drug therapy decisions for those with moderate to severe COVID-19 infections are extremely challenging at this time as evidence is limited.

Our understanding of best treatment practices is rapidly evolving. During this time of crisis, we have arguably entered into a period of "treatment" information overload. Data on potential treatments and associated outcomes are being released across a multitude of outlets. Typical of this media and literature overload, caution is advised as some outlets are more credible than others. It is critically important that we stay abreast of all the new treatment information and critically review the primary data sources. The emerging excitement with the recent French study that evaluated hydroxychloroquine and azithromycin as a treatment of SARS-CoV-2 infection is a perfect example of the need to investigate the primary data.[4] Across numerous media outlets, this combination has been an identified as a "game-changer." While results appear compelling on the initial read, it is important to recognized that it was an open-label single-arm study. Patients who refused the treatment met an exclusion criterion or did not receive hydroxychloroquine served as controls. Clearly, this algorithm for identifying control patients could have resulted in a biased comparison group. Furthermore, 26 patients were enrolled to received hydroxychloroquine yet only 20 were included in the analyses; six were excluded as they were lost to follow-up. Closer inspection of these six patients revealed that three were transferred to the intensive care unit, one died, one left the hospital, and one stopped treatment due to nausea. The results of the 20 included patients showed that those treated with hydroxychloroquine had significantly higher rates of virologic cure, defined as negative polymerase chain reaction (PCR) results in nasopharyngeal samples, relative to the controls (70% vs 12.5%, respectively, p-value = 0.001). Virologic cure rates were particularly impressive (100%) in the group that received both hydroxychloroquine and azithromycin. While the results of the 20 included patients are encouraging, inclusion of the six patients lost to follow-up would result in a very different interpretation of the results and indicate that the failure rate was approximately 40–50%. This study was only conducted respiratory PCR testing and it appears COVID-19 colonizes other body sites, including the gastrointestinal tract. Several of the control patients tested negative at baseline and detected positive at day 2 or 3, indicating the potential for differences between controls and cases in viral loads at baseline or within the first 24–72 hours. Last, hydroxychloroquine dosage was 200 mg every 8 hours, which is different than the currently

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recommended COVID-19 dosage regimen of 400 mg every 12 hours loading dose followed by 200 mg every 12 hours.[5, 6] Collectively, these findings call into doubt the effectiveness of this therapy, especially its ability to neutralize cytokine storm syndrome,[7] which is believed to be responsible for adult respiratory distress syndrome, organ dysfunction syndrome (MODS), and death in critically ill patients with severe disease. Furthermore, inappropriate application of these findings could result in a clinician using hydroxychloroquine and azithromycin in patients with a clear contraindication to therapy in their risk-benefit assessment of use. The major concern with hydroxychloroquine and azithromycin is prolonged QT syndrome, especially in patients with hepatic, renal dysfunction, immunosuppression, or receiving an additional QTc-prolonging agent(s).[2, 3] Based on data to date, this "at-risk" adverse event population is consistent with many of the patients with SARS-CoV-2 infection.

We can aid substantially in the care of patients with SARS-CoV-2 infection and contribute to the larger clinical community by publishing the treatment-related outcome findings of our COVID-19 patients. If data are amassed on COVID-19 patients, it is important that detailed information is collected on the outcomes associated with the treatment strategies used at our respective institutions. Ideally, we need to ensure that information collected is standardized across all patients. Treatment(s) received, baseline comorbidities, and concomitant therapies must be accurately captured. Receipt of treatment in relation to onset of symptoms must be documented given the critical importance of timeliness of therapy. Most importantly, a core outcome set is necessary. One of the major dilemmas associated with evaluating the current COVID-19 treatment literature is the inconsistency of outcomes reporting. In a review of 19 clinical trial registry platforms of COVID-19 clinical studies, 126 outcomes from 17 outcome domains were reported; almost half of outcomes were reported only once.[8] Clearly, there is a need to ensure that the most appropriate outcomes are collected and time to event outcomes (e.g., clinical response, virologic eradication, time on mechanical ventilation, time to hospital discharge, etc.) are collected in a serial fashion. One of the most important endpoints is changes in viral load. However, it is difficult to assess virologic response at this time with current RNA-based diagnostic tests. The PCR methods currently used are qualitative, not standardized to measure viral loads, and cannot distinguish between presence of active virus (live vs. dead).[9] Currently, there is no quantitative molecular test commercially available to determine viral load in response to therapy but one is likely to be available in the near future.

Given the multiple outcomes of interest in our COVID-19 patients, it may be advisable to create a desirability of outcome ranking (DOOR) endpoint.[10] Assessment of treatment effects using DOOR weighs both clinical and process measures to inform the clinician with the probability that the intervention will result in a positive patient-centered-outcome. Rather than looking at each outcome individually, all outcomes are merged into a list of potential overall clinical outcomes (based on benefits and harms) in DOOR and patients are ranked by the desirability of the associated overall outcome. The CRACKLE-2 prospective cohort study is a good example of the utility of DOOR.[11] In this study, the DOOR assessment included three deleterious events (absence of clinical response, unsuccessful discharge, and grade 3 and 4 adverse events; 30 days after the index event). The best outcome was defined as being alive without deleterious events and the worst as death. The three categories between these two extremes were alive with one, two, or three deleterious events. This DOOR definition can be readily adapted to assess treatment responses in our COVID-19 patients and ensure uniformity of outcome assessments across our investigations.

We should also consider collecting pharmacokinetic (PK) data on the treatment agents used in our COVID-19 patients. The PK of currently used agents is largely unknown in our COVID-19 patients. It is likely that many of the severely ill patients have augmented renal clearances and may need doses larger than anticipated due to enhanced clearance. Conversely, most of the patients with COVID-19 have underlying conditions that may alter the distribution and clearance of drugs. Given the potential for adverse events with the agents currently used (i.e., QTc prolongation with hydroxychloroquine), it is important that we try to understand the exposure-effect relationship as best as possible. This will aid in understanding if any of the observed clinical failures/adverse events are due to under-/overdosing. When possible, it would also be prudent to monitor changes in inflammatory markers like IL-6 in response to therapy and model the relationship

between drug exposure and changes in inflammatory markers over time.

Lastly, we are not alone in this battle and we must work together. We need to share best practices and lessons learned with each other. We should strongly consider collaborating with other institutions to develop a uniform approach to collect data and assess outcomes. This will allow for more robust treatment comparisons and an increased ability to draw meaningful and generalizable conclusions. The initial experience with lopinavir–ritonavir is a prime example of the critical importance of active collaborations and publication our collective experiences. Despite data suggesting that lopinavir–ritonavir was active against SARS-CoV-2 infection, no benefit was observed with lopinavir–ritonavir treatment versus standard care in a study of hospitalized adult patients with severe COVID-19.[12] If these results were not published, patients would have continued to receive this non-optimal therapy based on the mere promise of improved outcomes.

In conclusion, it is critically important that we ensure the most optimal therapy is delivered to COVID-19 patients in an expeditious fashion. Drug therapy decisions for those with SARS-CoV-2 infections are extremely challenging at this time, as evidence is limited. A number of candidate agents with activity against SARS-CoV-2 have been identified. It is our duty to critically evaluate these agents and work together to identify their proper placement in practice. We must share best practices and, when possible, collaborate with others to generate evidence on the real-world outcomes associated with available treatments. Publication of our experiences will benefit all future patients with COVID-19 and ensure that they receive the best available therapies.

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