MAYO CLINIC

Time to Treat: Applying Lessons Learned from Other Viral Syndromes to SARS-CoV-2

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Since the beginning of the coronavirus infectious disease 2019 (COVID-19) pandemic, the medical community has engaged in an ongoing search for safe and effective therapy for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This effort has been guided by the current understanding of viral attachment, replication, and subsequent immune hyperstimulation observed during coronavirus infection.[1] The current schema for clinical interventions includes supportive care, direct antiviral therapies, and immune modulation strategies targeting the cytokine release syndrome. Multiple therapeutic agents, both novel and repurposed, are approved under emergency use authorizations or under investigation, with early frontrunners in the United States being remdesivir, convalescent plasma therapy (CPT), hydroxychloroquine, and lopinavir/ritonavir (LPV/r). The bulk of published COVID-19 literature to date has consisted of small observational studies, early reports of larger-scale retrospective data, and few randomized, controlled clinical trials. Given the frequency of methodologic limitations to much of the available evidence, careful interpretation and application of this data has been required by health care practitioners worldwide. A key observation from the available data is that patient groups with more rapid antiviral intervention generally experience better outcomes.

TIME TO THERAPY INITIATION

The median time to therapy from the onset of symptoms in most interventional studies is more than 7 days, with some greater than 10 days. This is largely driven by a trial design that targeted hospitalized patients with hypoxia and requirement of respiratory support. Therefore, antiviral intervention was often delayed until after respiratory decompensation was observed, indicating that patients might have passed from the acute viral phase into the hyperinflammatory phase of the illness. With few exceptions, time until initiation of therapy was not explored as an independent variable in outcomes analyses. When time to therapy was incorporated into statistical analysis, patients designated in "early therapy" groups still often had prolonged (ie, 7-12 days) time to therapy initiation or the analysis did not account for the time since symptom onset until presentation.

HISTORICAL CONTEXT AND APPLICATION TO COVID-19

Data from other respiratory viral infections, such as influenza, suggest the greatest benefit of antiviral therapy when given earlier during infection.[2] Targeting a viral replication earlier during the illness is anticipated to influence the immune response and temper the progression to severe disease. In theory, this might also hold true for SARS-CoV-2, where earlier initiation of antiviral therapy during the early postexposure, minimally symptomatic phase, being likely to result in the greatest possible clinical benefit in the form of shortening the duration of illness, viral shedding, modulating the immune response, and subsequent prevention of hospitalization. The natural progression of the COVID-19 clinical course allows for a window of time between symptom onset and subsequent progression into the pulmonic and hyperinflammatory phase, which usually occurs around 7 days.[3] An early initiation approach could be particularly helpful in patients with multiple risk factors for severe illness, and, beyond individual patients, benefits may be seen in the dynamics of transmission in the community. Current evidence, albeit limited, appears to support this theory. For example, a study from China demonstrated that patients who received treatment

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within 6 days of symptom onset demonstrated shorter times to viral clearance compared with those who received later therapy initiation. Interpretation of the data remains difficult given the selected endpoints and the fact that patients in the study received various antiviral treatments, the primary of which (ie, arbidol) is not widely available.[4] Studies involving applicable individual therapies should be scrutinized closely for time to effective therapy.

REMDESIVIR

A randomized, placebo-controlled trial by Wang et al[5] evaluated the efficacy of remdesivir in patients with COVID-19.[5] In this study, the median time to therapy initiation from symptom onset was 10 days (interquartile range [IQR], 9-12 days). Time to therapy initiation from hospital admission was not reported. Mortality at 28 days was numerically higher in the placebo group compared with the early treatment group (≤10 days); however, this did not reach statistical significance. There was numerically higher mortality in the late treatment group (>10 days) compared with the placebo group, also not reaching statistical significance.[5] In the subsequent randomized clinical trial by Beigel et al,[6] median time to therapy initiation from symptom onset was 9 days (IQR, 6-12 days) and time to therapy initiation following hospitalization was not reported. They reported no difference in recovery rate between the early (≤10 days from symptom onset to treatment) versus late treatment (>10 days from symptom onset to treatment) groups.[6] Another clinical trial compared a 5-day versus 10-day course of therapy with remdesivir for the treatment of severe COVID-19.[7] The median time to therapy initiation from symptom onset was 8 days (IQR, 5-11 days) and 9 days (IQR, 6-12 days) in the 5- and 10-day groups, respectively. Discharge rates were 62% among patients who had symptoms for less than 10 days before receiving the first dose of therapy as compared with 49% in those who had symptoms for 10 days or longer.[7] A randomized, controlled trial compared 5- and 10-day courses of remdesivir to standard of care for the treatment of moderate COVID-19.[8] They demonstrated that 5-day courses, but not 10-day courses, were associated with improved clinical status on day 11. They did not compare outcomes by symptom duration before initiation, and both the 5-day and 10-day patients had symptoms for a median of 8 days before therapy, whereas standard-of-care patients had symptoms for a median of 9 days before randomization.[8] In addition, in two uncontrolled, open-label reports on the compassionate use of remdesivir, median time to therapy initiation from symptom onset was 11-12 days.[9,10]

CONVALESCENT PLASMA THERAPY

The premise of CPT is built upon the foundation of early administration. Seroconversion in SARS-CoV-2 infection occurs at a median of 11 days (range, 8-16 days) for immunoglobulin (Ig) G and 14 days (range, 8-28 days) for IgM.[11] Passive transfer of immunity, as in CPT, is presumed to be most effective when the patient has either no antibodies or subneutralizing antibody concentrations at the time of transfusion. Most recently, a landmark report on the effect of CPT on mortality in 35,322 patients with COVID-19 was released by the National Expanded Access Program.[12] Time to transfusion from diagnosis, not symptom onset, was evaluated. It was demonstrated that earlier transfusion (ie, <3 days from diagnosis) resulted in lower 30-day mortality as compared to transfusion 4 or more days after diagnosis (8.7% vs 11.9%; $P < .0001$).[13] In a small uncontrolled study of 80 patients in Hong Kong during the 2003 outbreak of SARS-CoV-1, patients receiving CPT within 14 days of symptom onset and those who were seronegative at the time of transfusion experienced superior clinical outcomes.[14] A recent review of CPT in COVID-19 identified 5 studies, all uncontrolled, with a total of 27 patients. The time to therapy from symptom onset ranged from 6 to 50 days.[15] In addition, a small uncontrolled study of 25 patients receiving CPT had a median time from symptom onset to transfusion of 10 days (IQR, 7.5-12.5 days) and hospitalization to transfusion of 2 days (IQR, 2-4 days).[12] In one randomized trial to date, patients were administered CPT in addition to standard of care.[16] Despite median times to hospital admission from symptom onset of 12 days for CPT patients and 10 days for control patients, the time to transfusion from onset of symptoms was 33 days (IQR, 20-39 days) for patients

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with severe and 26 days (IQR, 20-36 days) for patients with life-threatening disease. Only 5 patients with severe and 3 patients with life-threatening disease underwent transfusion within 14 days of symptom onset. The results did not demonstrate an overall benefit of clinical improvement within 28 days across all patients, and data were not analyzed by time to transfusion. However, there was a signal possibly toward superior outcomes in those with severe disease as compared to those with life-threatening disease, potentially pointing to a greater CPT benefit when given closer to the viral phase of the disease.[16]

LOPINAVIR/RITONAVIR

Although LPV/r has largely fallen out of favor in the treatment of COVID-19, studies exploring its use reveal pertinent findings. An open-label, randomized controlled trial evaluating LPV/r monotherapy versus standard of care initiated therapy after a median of 13 days (IQR, 11-16 days) after symptom onset.[17] They showed that early initiation (<12 days from symptom onset) resulted in a numerically lower mortality rate as compared with standard of care, although this did not reach statistical significance. The time between therapy initiation and hospital admission was not reported.[17] A multicenter, prospective, open-label, randomized trial, comparing LPV/r monotherapy to LPV/r combined with interferon beta-1b and ribavirin had a median duration between therapy initiation and symptom onset of 4 days (IQR, 3-8 days) in the monotherapy group and 5 days (IQR, 4-7 days) in the combination therapy group.[18] They demonstrated positive effects on virologic outcomes with combination therapy (median time from enrollment to negative nasopharyngeal swab of 7 days combination therapy vs 12 days control [$P = .001$]) and clinical recovery (median time to national early warning score [NEWS2] of 0 of 4 days combination therapy vs 8 days control [$P < .0001$]). This finding was most pronounced in patients that received treatment within less than 7 days from symptom onset. Notably, early intervention was part of this trial design, as they required patients in the intervention group to have initiated therapy within 48 hours of hospitalization.[18] Another study evaluated the duration of viral shedding in 181 patients with COVID-19 who received LPV/r monotherapy, LPV/r with interferon alpha, or LPV/r with interferon alpha and arbidol. They observed a shorter duration of viral shedding in patients receiving the combination of LPV/r with interferon as an initial regimen and in patients who had antivirals initiated within 5 days of symptom onset.[19]

HYDROXYCHLOROQUINE

Early data with hydroxychloroquine illustrate the shortfall of prolonged periods of time until drug initiation and lack of analysis on timing effects on outcomes. Time to therapy initiation has varied widely in COVID-19 hydroxychloroquine studies to date, with one open-label randomized controlled trial demonstrating a median time to therapy initiation of 16.6 days (range, 3-41 days).[20-22] In much of the hydroxychloroquine data, outcomes were not routinely analyzed by time to therapy initiation. Perhaps the ultimate measure of the effects of time to therapy initiation on outcomes is the evaluation of the utility of an agent before the development of symptoms (ie, as postexposure prophylaxis). The failure of hydroxychloroquine to demonstrate a benefit when used as postexposure prophylaxis provides perspective regarding the overall lack of efficacy of this agent in the treatment of COVID-19, and it makes evaluation of time to therapy initiation of little benefit.[23]

SUMMARY OF THE EVIDENCE

When evaluating the literature pertaining to the efficacy of therapeutic agents in COVID-19 clinicians should carefully consider the time to initiation of therapy. Available evidence would seem to suggest that, similar to evidence from other viral illnesses, when a benefit is observed it is generally optimized with initiation of therapy earlier in the course of illness. Careful attention to the time to therapy initiation metrics used in various studies will serve to further inform interpretation of the literature, as time to initiation could be reported from symptom onset, diagnosis, or study enrollment.

CHALLENGES AND FUTURE DIRECTION

We acknowledge the multiple challenges with early initiation of antiviral therapy, especially within the context of currently available agents and our understanding of their application to patient care. These challenges include the

need for intravenous access (ie, remdesivir), potential toxicities and drug-drug interactions, and considerations related to appropriate allocation of resources, especially in the context of high patient volumes. Beyond improved understanding of the efficacy of antiviral therapies, development of a validated risk prediction tool to identify patients at high risk for disease progression and aid with selection of those who might most benefit from early initiation of therapy would be ideal. We encourage clinicians to carefully consider time to initiation of antiviral therapy from symptoms onset when evaluating and applying emerging literature surrounding the treatment of COVID-19. Furthermore, until a SARS-CoV-2 vaccine is available, in order to optimize the available pharmacologic tools in battling the current pandemic, we advocate for researchers and clinicians alike to aim to shorten the time from the onset of symptoms until antiviral initiation, particularly in patients at high risk for disease progression.

Abbreviations and Acronyms: **COVID-19** = coronavirus infectious disease 2019; **CPT** = convalescent plasma therapy; **Ig** = immunoglobulin; **IQR** = interquartile range; **LPV/r** = lopinavir/ritonavir; **SARS-CoV-1** = severe acute respiratory syndrome coronavirus 1; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2

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