Brief on Triple Combination Therapy for COVID-19 Trial

A May 2020 publication from investigators in Hong Kong has gained attention for a triple-drug combination regimen for managing COVID-19. This open label, randomized, phase 2, multicenter study compared lopinavir/ritonavir to the combination of lopinavir/ritonavir plus ribavirin plus interferon beta. Based on initial reports of faster time to PCR negativity and clinical improvement, there may be interest in using such combinations in hospitalized patients with COVID-19 given the lack of approved treatment regimens to date. There are several study elements that limit the applicability of these results to US community hospitals that warrant highlighting.

First, while this study was performed in hospitalized patients, unfortunately, this group does not compare well with the patients hospitalized for COVID-19 in the US. In Hong Kong, every patient with a positive COVID-19 test was hospitalized; therefore, these patients entered the hospital and study very early in their clinical course. The median day of treatment initiation for the control group was day 4 following symptom onset and day 5 for the combination group. Severity of disease was assessed using the National Early Warning Score (NEWS2). At baseline, study patients had a median NEWS2 score of 2; few of these patients would meet current admission criteria for COVID-19 disease in the US. For example, a fever of greater than 102°F alone earns two points on the scoring rubric.

In an open label trial like this, it is important to focus on objective outcomes that cannot be swayed by clinician bias, such as mortality and time to PCR test negativity. Given the low mortality in the cohort (zero), the investigators opted to use time to PCR negativity. Among the patients receiving treatment within 7 days of symptom onset, patients in the combination group had a significant difference in time to PCR negativity compared to the control group (7 vs 12 days, HR 4.37, [95% CI 1.86-10.24], p=0.0010). The primary outcome of time to PCR negativity is interesting, but it is unclear how this correlates with clinical improvement. Further, it has been well described that patients can remain PCR positive for long periods after disease recovery, therefore making the clinical significance of this outcome unclear. The investigators also describe secondary outcomes such as daily SOFA and NEWS2 scores, time to achieve NEWS2 score of 0, and length of stay that all showed improvement in the combination arm compared to control if treatment was initiated within 7 days of symptom onset.

If you take this trial as it stands, it shows there is likely a benefit in early treatment of COVID-19 and a benefit of the combination therapy if given within 7 days of symptom onset over lopinavir/ritonavir alone in time to PCR negativity and symptom resolution. Whether this effect is due to early treatment initiation or a combination including interferon remains unclear. In the protocol, patients beginning treatment after 7 days of symptom onset did not receive the interferon component of the combination regimen and instead received lopinavir/ritonavir with ribavirin due to the concern for proinflammatory effects of interferon beta.

While the results of this study warrant further investigation of interferon beta and ribavirin for early treatment of COVID-19, the population studied is not representative of the current US inpatient population with COVID-19. Further, it is not practical or feasible to administer these agents to our non-hospitalized patients with COVID-19 that have mild to moderate symptoms.

This trial is a well-performed trial in the midst of a pandemic, but as many good studies tend to do, it may create just as many questions as answers. We do not currently think this study justifies adding interferon beta and ribavirin to your local treatment guidelines at this time. Please do not hesitate to reach to your DASON pharmacy liaison if you have further questions or discussion.

Reviewed on 5/18/20.

References: