MJH life sciences™ COVID-19 Coalition

Five Takeaways from

"Navigating the COVID-19 Treatment Landscape

Clinical Controversies Explained"

The coronavirus disease 2019 (COVID-19) pandemic has changed the landscape for infectious disease treatments, with drug developers and investigators racing to identify, develop and test therapies for the disease caused by the SARS-CoV-2 virus.

In the third of its biweekly series of webinars, the MJH Life Sciences™ COVID-19 Coalition, a partnership with top health care thought leaders across a variety of medical disciplines, addressed some of the considerations and controversies surrounding COVID-19 treatments.

The event was moderated by Jason M. Pogue, a clinical professor at University of Michigan College of Pharmacy, and included Jason Gallagher, a clinical professor at Temple University School of Pharmacy, and Susan Davis, a clinical professor at Wayne State University. Each holds a doctor of pharmacy.

"The treatment landscape is rapidly evolving," Pogue said. "It seems like every day, some new piece of information comes out, whether it be true or false. There's a lot of new literature. We're all constantly digging through that and trying to figure out how to best treat our patients. From things like antiviral therapy to immunomodulatory therapy to whether or not we should be using convalescent plasma or monoclonal antibodies, there are a lot of treatment controversies or considerations out there."

Gallagher and Davis serve on the Infectious Diseases Society of America (IDSA) and the National Institutes of Health (NIH) treatment guidelines panels, respectively, but both stressed that they were speaking independently during the webinar and not representing the panels.

What follows are five key takeaways from the webinar.

1. Final results of the ACTT-1 trial didn't change thinking about the antiviral drug remdesivir.

Preliminary results of ACTT-1 helped the Gilead Sciences therapy receive emergency use authorization in early May. Finalized data[1] showed that patients who received remdesivir had reduced time to recovery by an average of 5 days and lower respiratory tract infections compared with those who received a placebo.

"The mortality differences were seen at day 15 but not at day 29," Davis said. "So, at this point, dexamethasone might be the thing people still consider as the only quote(-unquote) proven mortality benefit. But mortality is not the only outcome that matters to our patients, certainly not the only outcome that matters to our health system infrastructure, so those differences that we see by severity and those differences that we see in hospital stay and time to recovery — I think those are still meaningful."

She also pointed out that looking at the outcomes by severity of disease is informative, noting that the benefits of the drug decreased as severity of disease at baseline increased.

However, disease severity exists on a continuum, and it can be difficult to assess where patients fit in terms of those categories.

Gallagher said that although he hoped that the data would show significant mortality benefit, overall, the final report was very similar to the preliminary data. He also said that duration of symptoms didn't seem to predict outcomes.

"I don't want clinicians to have to be in a difficult patient interview about duration of symptoms," he said. "The onset of this can be rather insidious or it can be abrupt. Having to figure that out on a patient-by-patient basis so they can come up with some magical cutoff that just fits this binomial variable I don't think is a good practice."

2. Exceptions to remdesivir guidelines should be considered.

NIH and IDSA guidelines don't recommend remdesivir for patients who don't require supplemental oxygen. Gallagher said clinicians shouldn't look at the guidelines as hard-and-fast rules.[2,3]

"There are areas where the benefit is very clear, and there is this area, which is not requiring oxygen, where that benefit is less clear," he said, adding that he doesn't think guidelines should be written in a way that suggests the drug should be used as a standard of care given to everyone.

"That's something that I don't think we should be saying," Gallagher said. "Do I think there are patients for whom it should be given? Absolutely. Someone who is 74 years old and obese

with other risk factors for progression to severe disease is very different from someone who is 30 years old and trim."

Davis said she doesn't think there is strong enough evidence to suggest for or against remdesivir for patients who don't require supplemental oxygen.

"We would expect these patients to get better, right?" Pogue said. "For the most part, patients…who are breathing fine — we expect most of them to get better. What we want to stop is the progression in those that are going to progress."

On the other hand, guidelines call for remdesivir in severe cases of COVID-19, but studies haven't demonstrated the benefits in these cases.

"I do not have a for or against answer on this, personally," Davis said. "I think there (are) still additional data that (are) necessary, and I will be interested when we have a larger study sample."

Factors that play into decisions about which patients should be treated with remdesivir include the use of steroids such as dexamethasone and the availability of the drug, which was limited early in the pandemic but has since become more readily available.

3. Steroids may have benefits for patients who require low levels of supplemental oxygen.

Data from the RECOVERY trial[4] showed that dexamethasone was beneficial to patients requiring ventilation or supplemental oxygen but didn't help those who didn't require supplemental oxygen.

More research is needed to determine breakpoints for treatment, Davis said.

"In the continuum of disease, from antiviral to anti-inflammatory, these patients are in the middle, and they have the potential to benefit from steroids, as we're seeing in some of these subsets," she said.

Gallagher said that much remains to be learned about the physiology of the disease and urged caution when talking about phases of disease, saying clinical data should be followed when available.

"There's a difference between that person that gets a little touch of the oxygen as they first come in and someone who comes in looking sick and you're worried about them progressing, and you're going to crank it up to the degree that you can before going to something more

invasive," Gallagher said. "Obviously, those are different people. But, honestly, even with them both falling into this overall bucket, I'm fine with giving steroids to them. The overall benefit is there, and I'm OK with that."

Although dexamethasone is administered for up to 10 days, once it's not needed, it can be stopped.

4. The outlook for convalescent plasma is complicated.[5-7]

"Convalescent plasma is both exciting and kind of a mess, I hate to say," Gallagher said. "That's just the nature of what it is."

An expanded access program at Mayo Clinic[5] included more than 35,000 patients, but it wasn't randomized and didn't include a comparator, making it difficult to interpret.

"There's interesting stuff to infer from the data about the higher concentrations of neutralizing antibodies versus lower ones and the time, how quickly someone received it after they had symptoms. But there's no comparator, and it just made it sort of a brutal distinction," Gallagher said. "I fall into this difficult and confusing place of (where) I think there's likely benefit. I certainly would use it in some people. But I can't tell you exactly who those people are, and I also have the concern with antibody therapies in general: How do we get them in people soon enough to make a difference?"

Limitations of the PLACID trial[6] in India include the level of testing done to select the plasma to be administered and the fact that the study wasn't blinded, Davis noted.

Some variables that might affect the outcomes of convalescent plasma[7] therapy include whether the patients are seropositive and the level of antibodies in the plasma, Pogue pointed out.

5. Monoclonal antibodies might be the next big therapeutic intervention.

"Eli Lilly and Company and Regeneron Pharmaceuticals are developing antibody therapies, but data are thus far limited to what's available in press releases.

"What was really interesting to me with their press release was the impact of whether or not the patient already had antibodies or not, whether they were seropositive or seronegative, the degree of viral load," Pogue said. "When you put these together, there is a suggestion that there is an ideal patient that this should be given to."

These therapies could potentially be administered in outpatient settings to patients with mild disease to prevent disease progression and the need for other treatments such as remdesivir and steroids, Pogue said.

A phase 3 trial of Lilly's monoclonal antibody treatment was paused because of safety concerns, underscoring the importance of clinical trials and the regulatory process for drug development.

"I do think prioritizing studies of these types of products is vitally important," Davis said. "I think as we look toward the future, things for prevention, particularly post-exposure prophylaxis, are going to be totally essential to getting

back to normal and preventing further spread. So, I am glad that we're seeing some of the preliminary data from these things. But advocating for therapy based on (a) press release makes me extremely uncomfortable.

"I feel like maybe that was happening early on in the pandemic, but I don't want us to continue doing that. These press releases give a signal, predominantly for investors, not so much for me. I can't act based on this."

A potential obstacle to these treatments is that they could be logistically difficult to administer if they are offered as IV infusions, Gallagher pointed out.

"I think what we desperately want besides a vaccine in COVID therapeutics is something that prevents that person from progressing, and that's hopefully what these may be — caveat, caveat," he said.

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