Hope for Critically Ill Covid-19 Patients-Hanging on a p-Value

On March 30th, CytoDyn Inc., a US biotech, released results from a Covid-19 study indicating an unprecedented 82% reduction in death measured at Day 14 in a group of 62 critically ill patients (ie, on a ventilator) who received a drug called leronlimab compared with a placebo. This marks the first time any treatment has demonstrated improved survival in intubated Covid-19 patients in a randomized, double-blind, placebo-controlled study, the gold-standard of clinical medicine. This striking result aligns with published reports of other critically ill Covid-19 patients successfully treated with leronlimab under compassionate use programs.

Unfortunately, this is where things get a bit complicated. The "p-value", or test of statistical significance of the 82% survival benefit, was reported as 0.023 which, being less than 0.05, would normally indicate the result had a less than 1 in 20 chance of having randomly occurred. However, these patients were only a "subgroup" within the larger CytoDyn study that included many more patients with less severe illness in whom the benefit of leronlimab remains uncertain. As a result, the overall study did not meet criteria for statistical significance. The p-value for the critical subgroup is part of a "post hoc" data analysis and therefore not considered sufficiently robust to meet the threshold for drug approval. In order to prove the claim, CytoDyn needs to enroll a new study of just critically ill patients that will take months to complete. In the meantime, the FDA has refused to approve CytoDyn's request for an Emergency Use Authorization (EUA). The consequences of this decision for critically ill Covid -19 patients, their ICU medical teams, and the US economy during a new wave of infection due to mutant strains of virus could be disastrous.

The FDA is given the authority to exercise judgement and issue an EUA in the setting of an urgent unmet medical need when available evidence suggests a treatment will provide more benefit than harm. The agency has issued EUAs for other Covid-19 therapies that directly attack the virus but are only effective if given early in the course of illness. None of the antiviral therapies have proven to help patients during the latter or "hyperinflammatory" stage of the illness during which a disordered immune response, rather than the virus itself, appears to drive complications including death. Dexamethasone, a potent steroid, is thought to help but has not been tested in a double-blind, placebo-controlled trial in this patient population.

In contrast to antiviral approaches, leronlimab is a monoclonal antibody that treats the latter stages of Covid-19 illness including pneumonia by disrupting signals within the body that create inflammation. In one remarkable case, a patient in London on life support for 2 months began weaning off that support just 4 days after receiving his first dose of leronlimab. Though anecdotal, this case underscores the dramatic benefit that can be seen in some patients. Importantly, since the mechanism of action is independent of the virus, leronlimab should remain effective in patients harboring mutant virus.

On the other side of the EUA calculation is the important question of safety. Here too, the FDA's inaction is difficult to understand. Leronlimab has been safely administered to more than 1200 patients, including patients in studies of HIV, cancer, and Covid-19. Some patients with HIV have received the drug by injection under the skin weekly for up to six years without any discernable safety issues.

We write today as a group of physicians with no equity stake in CytoDyn. We have published in peer-reviewed journals on outcomes of other critically ill patients treated with leronlimab. The drug was obtained for these patients through various cumbersome and restrictive individual compassionate use programs. The striking survival benefit suggested by the leronlimab study fully aligns with our own experience. We are convinced the drug can mitigate the effects of a disordered immune response in many critical Covid-19 patients and give those patients and their medical teams a fighting chance. The evidence also suggests the drug causes no harm in those it doesn't seem to help.

Crucial questions remain. The survival benefit in the CytoDyn study disappointedly tapered off from 82% compared to placebo at Day 14 down to 24% at Day 28. The tapering of benefit may have occurred because patients were not given the drug for the final two weeks of the study per FDA guidance. What will overall survival be when critically ill patients are permitted to receive the full 4 weeks of dosing as originally proposed? Will administering the first dose by intravenous infusion achieve a more rapid onset of action in patients for whom every minute matters? Finally, why do some patients appear to respond to leronlimab while others do not? Studies are underway to answer these urgent questions.

In the meantime, the future of the pandemic remains deeply uncertain. Even as the US starts to reopen, we are confronting a growing surge of mutant strains that are more infectious, possibly more lethal, and likely a greater threat to younger individuals. The FDA has the authority and mandate to act with common sense in a crisis. Janet Woodcock, the acting Commissioner of the FDA, has opined on "the cost of failing to approve an effective therapy" when "there may be thousands of lives to be lost if you delay." Commissioner Woodcock tellingly added "people say

they want placebo-controlled trials, but I always ask them would you be willing to die to give a p-value?"

The current evidence is clear: leronlimab is safe and can save lives. The FDA should issue an EUA now while further studies are completed. Hope and relief for the sickest and most vulnerable among us cannot be held hostage to a p-value any longer.

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