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BRIEF19

A daily review of covid-19 research and policy

RESEARCH BRIEFING

Baricitinib and tocilizumab results by press release *and* Twitter release?

Two covid-19 treatment updates went live yesterday, one via press release while the other was announced on Twitter. (This is real). While there aren't any actual data or research abstracts to assess, critique, or comment on, some information can still be gleaned.

The first medication, **tocilizumab** (*TOE-see-LIZ-you-mab*) is a monoclonal antibody that targets a receptor in our immune system called interleukin 6 (IL-6), which plays an important part in the body's inflammatory response). In October, we covered the results of three relevant studies. One study was a multicenter retrospective cohort study in the United States called STOP-COVID. That study indicated a possible mortality benefit among patients admitted to intensive care units (ICUs) who received this medication. However, two randomized clinical trials (RCT) published on the same day, in the same journal, found no mortality benefit. The following day, we covered yet another RCT testing tocilizumab that was published in *The New England Journal of Medicine* which was also failed to show evidence of either efficacy or harm.

So, what's new? Investigators of the REMAP-CAP trial released news via Twitter regarding the efficacy of tocilizumab in their clinical trial. REMAP-CAP is a multicenter ongoing clinical trial assessing multiple interventions. REMAP-CAP is particularly notable because the patients enrolled in the study are all in ICUs, meaning they are the sickest hospitalized covid-19 patients. That said, yesterday they announced that based on interim results, the data safety and monitoring board "is declaring efficacy of tocilizumab with an odds ratio of 1.87 for benefit on a combination of survival and length of time patients received organ support in ICU, compared with standard care...with 99.75% probability of benefit for tocilizumab compared to no immune modulation." This implies that the effect of tocilizumab must be fairly robust to detect such a significant effect this early in the trial's enrollment period.

Next: **baricitinib** (*BEAR-uh-SIT-in-ib*), a drug used for the treatment of rheumatoid arthritis. Like tocilizumab, baricitinib is a monoclonal antibody that binds and inhibits the activity of certain proteins. The proteins baricitinib binds are called JAK1 and JAK2, which also play a role in the body's inflammatory pathway. Given that inflammation is thought to be a problem in covid-19, there is biological plausibility for a drug like this. The Food and Drug Administration (FDA) has issued an emergency use and authorization (for more on EUA approvals, look here) for the use of baricitinib in combination with remdesivir (*rem-DESS-uh-veer*) in hospitalized adult *and* pediatric patients with covid-19 requiring supplemental oxygen, mechanical ventilation or extracorporeal membrane oxygenation ("ECMO").

The FDA made the decision to provide EUA approval for baricitinib (in conjunction with remdesivir) based on data provided by the ACTT-2 trial, another RCT, sponsored by the National Institute of Allergy and Infectious Diseases (directed by Anthony Fauci). While data from ACTT-2 have not yet been published yet (the trial assesses patients admitted to the hospital with moderate to severe covid-19), the FDA reports that the median time to recovery from covid-19 was seven days in patients who received both baricitinib *and* remdesivir, versus eight days (one more day) in those who received placebo plus remdesivir. While numbers have not been provided, the FDA states that *clinical improvement* at day 15 and *survival* at day 29 was higher in receiving baricitinib plus remdesivir, and the data were supposedly statistically significant. As with tocilizumab, data and publications are forthcoming.

In sum, tocilizumab and baricitinib (plus remdesivir) were *announced* to be effective in patients hospitalized with covid-19. However, the data have not been npublished in medical journals and these statements should be viewed with skepticism. *—Joshua Niforatos, MD*

Remdesivir loses support from the WHO

Thursday evening, a new review from the World Health Organization was published by the *British Medical Journal*, entitled "A living WHO guideline on drugs for covid-19." This comprehensive document addresses drug interventions in treating covid-19 and this latest version focuses on the use of the anti-viral medication remdesivir. Sure to bring controversary to an already contentious topic is the new stance taken by the WHO which provided a "weak or conditional" recommendation on the use of remdesivir in hospitalized patients. Behind the new WHO stance (in direct opposition to the US FDA) are the results of the WHO Solidarity trial, released as a preprint in October. This over 11,000 patient multi-site multi-national study investigating not only remdesivir but hydroxychloroquine, lopinavir and interferon showed the drug had little or no effect on mortality, decreasing need for mechanical ventilation, or significantly changing hospital duration. Despite previous studies published in the *New England Journal of Medicine* the panel still felt that the extant available evidence is either low quality or low certainty and there is no current proof that remdesivir improves patient-important outcomes. An important clarification the authors made was this does that imply ineffectiveness. Rather, the sum of all current research shows a small and uncertain benefit that must be weighed against the harms. Consideration must be made of socio-economic factors such as equity, feasibility and resources across all healthcare systems worldwide. An accompanying editorial asks if remdesivir simply "Tamiflu redux"? Tamiflu (Oseltamivir) is an expensive influenza medication with limited benefit. Despite its widespread use, it has no real record of saving of lives.

However, The WHO Solidarity trial has been called into question by the drug manufacturer Gilead because it was "open label" (not blinded) and did not have a placebo. That may sound compelling but generally unblinded trials *favor* the intervention, as researchers and healthcare providers on some level "want" new treatements to work.

Will the WHO study tip the scales against the drug? It might. Its enrollment numbers far exceeded previous studies used to justify the use of remdesivir in covid-19 patients. That does not mean that the US FDA will change course though, though the agency has come under fire for its subpar appraisal of literature during the pandemic. One thing is certain; remdesivir does not appear to be the savior many hoped it would be. *—Christopher Sampson, MD, FACEP*

First coronavirus home test granted emergency use authorization.

On Tuesday the US FDA announced an Emergency Use Authorization (EUA) for the first rapid coronavirus home test. The Lucira COVID-19 All-In-One Test Kit test uses a nasopharyngeal swab sample that is run on the included device, with results available in 30 minutes. The test is available by prescription for ages 14 and up, with providers required to report all home test results to health department officials in accordance with applicable laws. In addition to the home standards, the EUA also allows the device's use in point-of-care settings, but a healthcare provider must collect the sample for patients under 14. This new at-home test adds to the growing list of easier, faster tests with EUAs aimed at closing the surveillance gap that has plagued accurate tracking during the pandemic. *The FDA.* *—Joshua Lesko, MD*

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