Good morning. Today's Briefing will be a more tradition format. I hope you found Monday's Briefing of value.

Today I start with news around vaccines and a timely announcement from the European Society of Intensive Care Medicine's (ESICM) statement on Remdesivir.

I then turn attention to a series of fascinating article on our expanding understanding of the immune response focused on IFN. I end with a provocative article on the use of fluvoxamine an antidepressant SSRI class and its potential mechanism for immune modulation as an σ-1 receptor (S1R) agonism.

Friday part of my focus will be on recent articles on duration of immunity after SARS-CoV-2 infection. Hint: it may be longer than we initial feared!

Have a great day and happy reading

Ed

COVID News

Vaccines

Moderna's vaccine against SARS-CoV-2, known as mRNA-1273, has shown 94.5% efficacy in an interim analysis from its phase 3 clinical trial announced on Monday. The trial has enrolled over 30,000 U.S. participants. In the interim analysis, 5 cases of COVID-19 were confirmed in participants who had received two doses of the vaccine, versus 90 cases in those who'd received a placebo vaccine. For severe COVID-19, there were no cases after vaccination — versus 11 cases with placebo. The data monitoring board identified no safety concerns. In addition, the company reported that the vaccine remains stable at 2° to 8°C (36° to 46°F) for 30 days: that is the temperature of a typical home refrigerator. mRNA-1273 is not expected to be widely available until 2021. This is different from Pfizer's vaccine which needs ultracold for storage.

In a follow-up Pfizer now has updated their final analysis and now says their vaccine is also 95% effective.

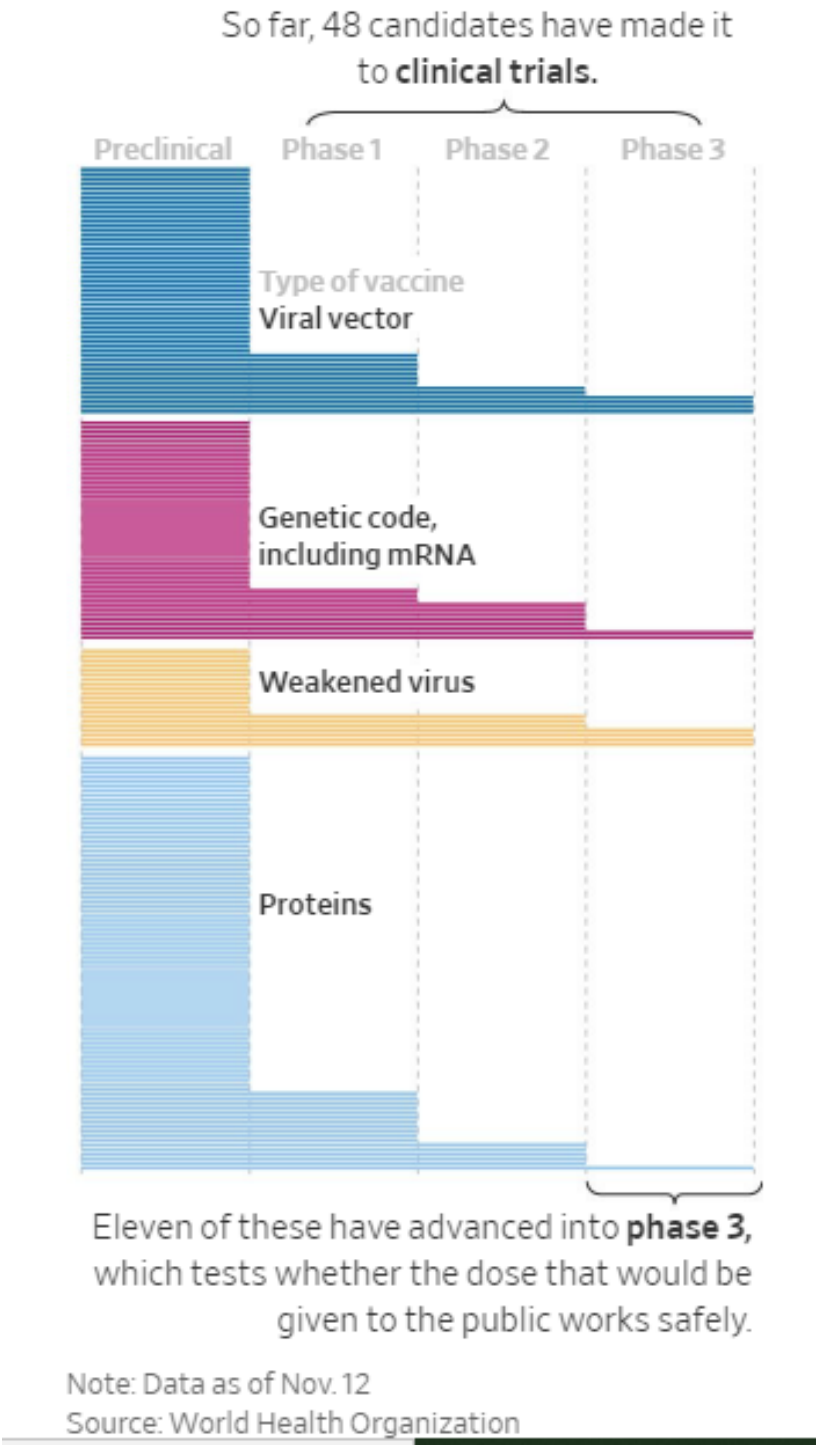
What we have learned is that companies can design mRNA vaccines relatively quickly once they know the genetic sequence of the pathogen. Researchers use the genetic sequence of a targeted virus to program the mRNA that can fight it. RNA appears to provide more stimulation of the immune system than other vaccine technologies both by generating antibodies and by inducing important responses from T-cells.

Vaccines from AstraZeneca and from Johnson & Johnson are based on a technology that uses a common-cold virus (adenovirus) vector to deliver genetic instructions that stimulates the human immune system to mount an immune response. The common-cold viruses are modified so they do not cause infections.

Merck is taking a more traditional approach by pursuing vaccines with proven technologies that employ an attenuated virus that multiplies to generate an immune response.

Despite the positive early results for the Pfizer and Moderna vaccines, a lot remains to be learned, including how long any apparent protection from Covid-19 lasts and how effective the vaccines are in certain high-risk populations such as the elderly. However, the positive data for mRNA-based Covid-19 vaccines bodes well for the technology's potential to combat future outbreaks of infectious diseases.

Below is the latest WHO tracking of COVID-19 vaccines.



European Society of Intensive Care Medicine (ESICM) Statement on Remdesivir

The largest study on remdesivir' s efficacy by the WHO (Solidarity), pre-published on Oct. 15 demonstrated little or no impact. The ACTT-1 Trial did not show benefit in ICU patients in sub analysis. Considering the new interim data from the WHO's Solidarity trial ESICM now classifies remdesivir as a drug you should not use routinely in COVID-19 patients. This recommendation will be discussed in a scientific paper on COVID therapies that ESICM is preparing with the Society of Critical Care Medicine.

Comment: It is time we admit that based on the science remdesivir appears to be a weak drug in our battle to treat SARS-CoV-2 infection. It is hard to ask physicians to wait for the evidence when there is a treatment that could hold some promise, especially in the midst of a pandemic. But the hasty approval and use of expensive new treatments like remdesivir is not the solution. We must follow the science even if it does not fit our narrative. Remdesivir probably does have a role in the early treatment of hospitalized COVID-19 before progression to the inflammatory stage. See the Daily Briefing last Monday for a full review.

JAK Inhibition Reduces SARS-CoV-2 Liver Infectivity and Modulates Inflammatory Responses to Reduce Morbidity and Mortality

Science Advances published November 13, 2020

In this study, a total of 83 patients were treated with baricitinib, a JAK inhibitor between mid-March and mid-April 2020. All patients enrolled had an SaO2 < 94% at baseline but did not require mechanical ventilation. Baricitinib was administered at a dose of 4 mg/day for 14 days in conjunction with standard of care in Italy, and at lower doses of 2 or 4 mg/day for 3 to 11 days in the Spanish cohort because of age-related factors. Eighty-three controls were included in the study using propensity score matching systems. Most individuals received concomitant antiviral therapy with hydroxychloroquine and lopinavir/ritonavir, antibiotics, corticosteroids and low molecular weight heparin.

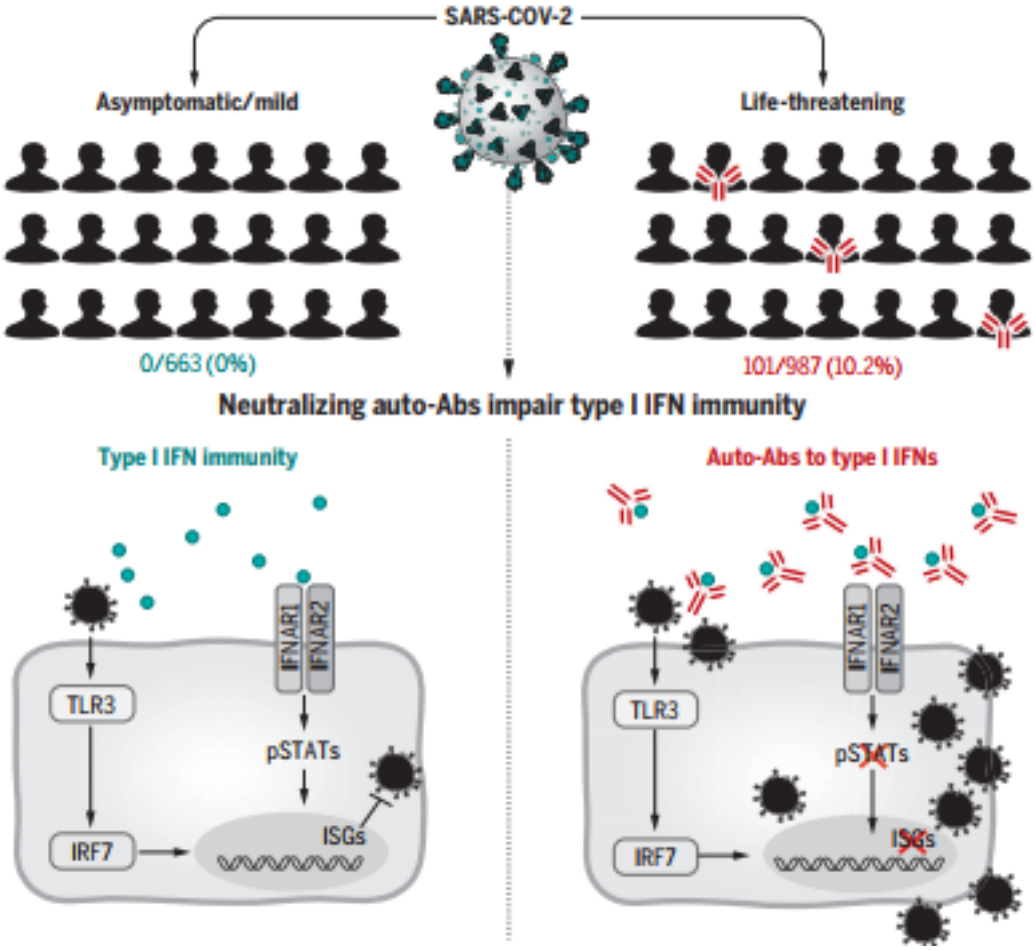
The study showed that the primary composite-endpoint of death or invasive mechanical ventilation occurred in 14 (16.9%) patients in the baricitinib-treated group compared to 29 (34.9%) in the control group ($P < 0.001$). In the multivariate Cox-regression analysis adjusted for all the covariates included in the matching of the two cohorts, baricitinib was independently associated as a protective variable with the primary outcome (hazard ratio [HR], 0.29; 95% confidence interval [CI], 0.15-0.58; $P < 0.001$).

Using organotypic 3D cultures of primary human liver cells, the researchers demonstrated that interferon-alpha-2 (IFNα2) significantly increases ACE2 expression and SARS-CoV-2 infectivity in parenchymal cells by >5-fold and exposure to therapeutically relevant concentrations of baricitinib fully abolished ACE2 induction by IFN-α2 and efficiently blocked the increased infectivity in cytokine treated 3D liver microtissues even beyond the levels observed in non-cytokine exposed samples. Further, RNA-Seq revealed gene response signatures associated with platelet activation were fully inhibited by baricitinib.

To evaluate the effects of baricitinib on replication and viral entry, the researchers analyzed viral loads at 4 hours post infection using baricitinib concentrations close to the relevant Kd values (100 nM). Super-resolution microscopy revealed anti-nucleocapsid protein immunoreactivity clusters throughout the infected samples. In contrast, virus signals were almost absent in baricitinib-treated samples, demonstrating that baricitinib efficiently blocked viral entry at nanomolar concentrations.

Comment: This study demonstrates the ability of baricitinib, a JAK/STAT pathway inhibitor, to inhibit viral entry and reduce inflammatory markers in COVID-19 patients, reducing mortality risk by 71% among patients with moderate-severe COVID-19 pneumonia. In addition, the study shows that baricitinib prevents the type-1 interferon (IFN) mediated increase in the expression of angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2. This study was not a randomized trial comparing baricitinib to a placebo control group; thus, known and unknown confounding variables could have compromised the results. In addition, this was a small sample size which could limit the overall statistical power. Nonetheless this is one of several trials with baricitinib reviewed in the Daily Briefing with promising results. An RCT is ongoing.

Autoantibodies Against Type I IFNs in Patients with Life-Threatening COVID-19
Science published online October 23, 2020
The investigators report that at least 101 of 987 patients with life-threatening COVID-19 pneumonia had neutralizing immunoglobulin G (IgG) autoantibodies (auto-Abs) against interferon-w (IFN-w) (13 patients), against the 13 types of IFN-a (36), or against both (52) at the onset of critical disease; a few also had auto-Abs against the other three type I IFNs. The auto-Abs neutralize the ability of the corresponding type I IFNs to block SARS-CoV-2 infection in vitro. These auto-Abs were not found in 663 individuals with asymptomatic or mild SARS-CoV-2 infection and were present in only 4 of 1227 healthy individuals. Patients with auto-Abs were aged 25 to 87 years and 95 of the 101 were men.

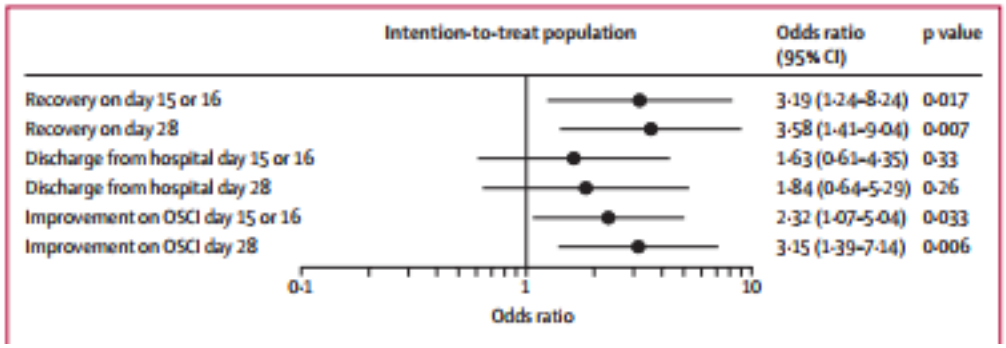


Comment: This is just another study trying to understand the immune system and SARS-CoV-2 infections. This study highlights the crucial role of type I IFNs in protective immunity against SARS-CoV-2. These auto-Abs against type I IFNs were clinically silent until the patients were infected with SARS-CoV-2—a poor inducer of type I IFNs—which suggests that the small amounts of IFNs induced by the virus are important for protection against severe disease. The neutralizing auto-Abs against type I IFNs, like inborn errors of type I IFN production, tip the balance in favor of the virus, which results in devastating disease with insufficient, and even perhaps deleterious, innate and adaptive immune responses. This finding paves the way for preventive or therapeutic intervention, including plasmapheresis, monoclonal Abs depleting plasmablasts, and the specific inhibition of type I IFN–reactive B cells. Injected or nebulized IFN-b may have beneficial effects, as auto-Abs against IFN-b appear to be rare in patients with auto-Abs against type I IFNs.

Safety and Efficacy of Inhaled Nebulised Interferon beta-1a (SNG001) for Treatment of SARS-CoV-2 Infection: A Randomised, Double-Blind, Placebo-Controlled, Phase 2 Trial
Lancet Resp Med published online November 12, 2020
The investigators performed a randomized, double-blind, placebo-controlled, phase 2 pilot trial at nine UK sites. Adults aged 18 years or older and admitted to hospital with COVID-19 symptoms, with a positive PCR or point-of-care test, or both, were randomly assigned (1:1) to receive SNG001 (6 MIU) or placebo by inhalation via a mouthpiece daily for 14 days. The primary outcome was the change in clinical condition on the WHO Ordinal Scale for Clinical Improvement (OSCI) during the dosing period in the intention-to-treat population (all randomized patients who received at least one dose of the study drug). The OSCI is a 9-point scale, where 0 corresponds to no infection and 8 corresponds to death. Multiple analyses were done to identify the most suitable statistical method for future clinical trials. Safety was assessed by monitoring adverse events for 28 days.

Patients were randomly assigned to SNG001 (n=50) or placebo (n=51). 48 received SNG001 and 50 received placebo and were included in the intention-to-treat population. 66 (67%) patients required oxygen supplementation at baseline: 29 in the placebo group and 37 in the SNG001 group.

Patients receiving SNG001 had greater odds of improvement on the OSCI scale (odds ratio 2·32 [95% CI 1·07–5·04]; p=0·033) on day 15 or 16 and were more likely than those receiving placebo to recover to an OSCI score of 1 (no limitation of activities) during treatment (hazard ratio 2·19 [95% CI 1·03–4·69]; p=0·043). SNG001 was well tolerated. The most frequently reported treatment-emergent adverse event was headache (seven [15%] patients in the SNG001 group and five [10%] in the placebo group). There were three deaths in the placebo group and none in the SNG001 group.



Common: Patients who received nebulized interferon beta-1a had greater odds of improvement and recovered more rapidly from SARS-CoV-2 infection than patients who received placebo. Interferons are cytokines that modulate immune responses to viral infection. The type I interferons (interferon-α and interferon-β) have been tested against coronavirus infections in vitro, with encouraging results. Interferon-β has been shown to be more potent than interferon-α. Patients with severe SARS-CoV-2 infection have been shown to suppress cellular interferon production, thus limiting the strength of the initial innate immune response. [see above articles] Exogenous use of inhaled interferon beta-1a in patients with asthma and respiratory viral infections has previously been shown to improve antiviral responses and improve lung function. This study serves as a proof of concept that inhaled interferon beta-1a could attenuate the clinical consequences of COVID-19. Larger studies in patients with COVID-19 are needed to further investigate the therapeutic potential of inhaled beta-1-a.

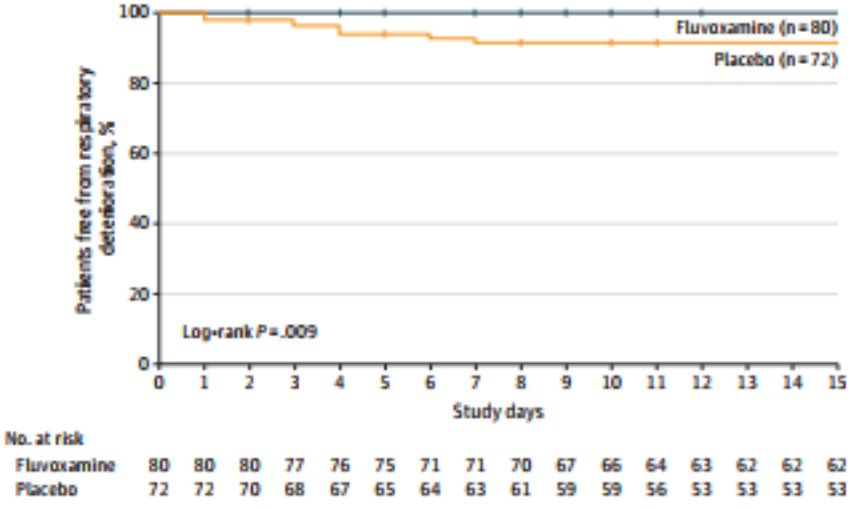
Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients with Symptomatic COVID-19 A Randomized Clinical Trial

JAMA published online November 12, 2020

In a small study 152 adult outpatients with laboratory-confirmed COVID-19 and symptom onset within 7 days were randomized to receive fluvoxamine 100 mg (n = 80) or placebo (n = 72) 3 times daily for 15 days from their home. Clinical deterioration was defined as having shortness of breath or hospitalization for shortness of breath or pneumonia AND oxygen saturation <92% on room air or need for supplemental oxygen to achieve oxygen saturation of ≥92%. Clinical deterioration -- the primary endpoint -- occurred in zero of the patients treated with fluvoxamine compared with 6 (8.3%) patients treated with placebo over 15 days, a difference that was statistically significant (*P* = .009).

Among the placebo group, cases of clinical deterioration ranged from 1 to 7 days after randomization and from 3 to 12 days after the onset of COVID-19 symptoms. Four of the 6 patients with clinical deterioration were hospitalized.

Figure 2. Time to Clinical Deterioration in the Fluvoxamine and Placebo Groups



Comment: A potential mechanism for immune modulation is σ-1 receptor (S1R) agonism. The S1R is an endoplasmic reticulum chaperone protein with various cellular functions, including regulation of

cytokine production through its interaction with the endoplasmic reticulum stress sensor inositol-requiring enzyme 1α (IRE1). Previous studies have shown that fluvoxamine, a selective serotonin reuptake inhibitor (SSRI) with high affinity for the S1R, reduced damaging aspects of the inflammatory response during sepsis through the S1R-IRE1 pathway, and decreased shock in murine sepsis models. [Sci Transl Med. 2019;11 (478):eaau5266] This study is limited by a small sample size and short follow-up duration, and determination of clinical efficacy would require larger randomized trials with more definitive outcome measures.