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Medical Intelligence Report

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Topic: Update on COVID-19 Research

Convalescent Plasma

The FDA authorized the general use of convalescent plasma for COVID-19 through an Emergency Use Authorization (EUA) on August 23 (Facher, 2020). Convalescent plasma is a component of blood that has been obtained from people who recovered from COVID-19. The plasma component of blood contains immune molecules, such as antibodies, that were produced by the immune system to combat the infection with SARS-CoV-2. Convalescent plasma is thought to help slow the production of virus until an individual's immune system is able to mount its own response.

Up to this point, treatment with convalescent plasma was only available as part of a clinical trial. There have been both traditional clinical trials to test the efficacy of the treatment and trials known as an expanded access program or "compassionate use trials" where unproven treatments can be used under the observation of the FDA. It has been difficult to recruit individuals to traditional clinical trials of convalescent plasma because potential participants have not wanted to risk receiving the placebo rather than the active treatment. Instead people have opted to participate in the expanded access programs.

Studies have determined that use of convalescent plasma is safe for use in individuals with COVID-19, but there are still some questions about the efficacy of the treatment with COVID-19 symptoms. The largest trial available evaluating the treatment was performed at the Mayo Clinic and included over 35,000 participants (Garde and Herper, 2020). However, the study did not include a placebo group, making it difficult to determine the absolute effect of the treatment. Also, the study results have not yet been published in a peer-reviewed journal. Individuals who received convalescent plasma within three days of diagnosis had a seven-day mortality of 8.7%, and individuals who received the treatment four or more days after diagnosis had a seven-day mortality of 11.9%, which was found to be a statistically significant difference. The participants in the study were often critically ill, with 52% in intensive care units and 28% requiring mechanical help to breathe. There was preliminary evidence that plasma from different sources had differing levels of effect as well (McGinley et al., 2020). The researchers measured the amount of antibodies in the plasma and found participants who got plasma with high-doses of antibodies were less likely to die than those receiving plasma with lower doses of antibodies.

Experts from the NIH argued for delaying the EUA for convalescent plasma due to a lack of definitive data showing that its use improves the outcomes of people with COVID-19 (New York

Times, 2020). Additionally, now that the treatment is available outside of clinical trials, it may be even more difficult to recruit participants for placebo controlled trials, making it difficult to determine the efficacy.

Remdesivir

A placebo controlled trial of remdesivir in moderately ill individuals was published in JAMA on August 21 (Spinner et al., 2020). A previously published study included participants who were more seriously ill and found that use of remdesivir led to a reduction in time before recovery from 15 days to 11 days.

In this trial, 584 participants with moderate disease defined as pulmonary infiltrates and room-air oxygen saturation higher than 94% were treated with either a 10-day course of remdesivir, a 5-day course of remdesivir, or standard care. The researchers reported that on day 11, participants in the 5-day remdesivir group had a statistically significant higher chance of having a better clinical status distribution than those receiving standard care. There was no difference in the clinical status between participants treated with 10-days of remdesivir and those that received standard care. There were few deaths in any of the groups with nine total deaths in the study after 28 days. The proportion of deaths in each group was 1% for those in the 5-day treatment group, 2% in the 10-day treatment group, and 2% in the standard care group.

> **Based on the results, the authors concluded that only the 5-day treatment group had a statistically significant difference in clinical status, but it is unknown what the clinical importance of this difference will be. Additionally, there was no difference in the mortality between the three groups.**

An accompanying discussion of the most recent paper and the previous studies stated that "there are now 3 RCTs [randomized and controlled trials] of remdesivir in hospitalized patients with differing results, raising the question of whether the discrepancies are artifacts of study design choices, including patient populations, or whether the drug is less efficacious than hoped." The third trial was an early trial that reported no benefit in people with COVID-19 with the use of remdesivir, but experts felt that the small number of participants may have influenced the outcome, making it difficult to observe an effect.

A potential issue discussed is the timing of treatment with anti-viral drugs such as remdesivir. In the two large studies, the treatment was started a median of nine days after the start of symptoms, which may be past the point where reduced viral production affects the disease outcome.

Other problems with the studies include the fact that they were not blinded, and both participants and the researchers were aware of who received which treatment. The assessment used is also a newly developed scale that seems to have issues that make it difficult to translate the outcome (called a summary odds ratio) into a clinically meaningful assessment of the treatment. Differing effects of the treatment on the different ends of the scale (death versus discharge from the hospital) can lead to cancelation of a net benefit from the treatment when they are combined. It is thought that this problem may have affected the evaluation of the 10-day treatment group in the Spinner and colleagues' study. Participants in the 10-day treatment

group were also less likely to finish the entire treatment than those in the 5-day treatment. Finally, the results of a study on the effects of the steroid dexamethasone were released in the middle of the remdesivir study, and the trial had not been designed to account for use of the steroid. The use of the steroid was not included in the analysis of the trial, and that could also have affected the outcome.

Changes in COVID-19 Testing

There were two changes to testing recommendations from the FDA and CDC. The FDA announced that they would no longer require premarket reviews of tests for COVID-19 that are developed by authorized laboratories (Galford, 2020). This policy only affects tests developed and used within a laboratory that has authorization to run complex diagnostic tests based on the Clinical Laboratory Improvement Amendments (CLIA), which is overseen by the Centers for Medicare & Medicaid Services.

> **Essentially, tests that will be commercially marketed for sale to other laboratories will still require assessment by the FDA, but laboratories that have been certified as meeting requirements for processing complex diagnostic tests will no longer be assessed as their competency is assumed from the CLIA authorization.**

This is the normal situation for CLIA authorized laboratories. However, during emergencies, the FDA enables access to medical countermeasures, such as diagnostic tests, through providing EUAs (FDA, 2020). Experts worry that the number of tests that are used to diagnose serious or life-threatening diseases or conditions is increasing, and that the results of the tests influence decisions on public health, requiring a higher level of regulatory oversight in general and specifically for the SARS-CoV-2 pandemic (Lim and Brennan, 2020). The FDA has stated that reducing regulatory oversight was crucial in the early weeks of the pandemic when the number of tests available was severely limited. Loosening oversight was seen as important in increasing capacity.

The CDC also released changes to their testing considerations for COVID-19 diagnostic testing (CDC, 2020). The changes were to the recommendations for people who have been in close contact with a person with a proven COVID-19 diagnosis.

Previously, the CDC stated that "**testing was recommended**" for individuals who "have been in close contact (within 6 feet) of a person with a COVID-19 infection for at least 15 minutes but do not have symptoms."

The recommendations now state, "If you have been in close contact (within 6 feet) of a person with a COVID-19 infection for at least 15 minutes but do not have symptoms: **You do not necessarily need a test unless you are a vulnerable individual or your health care provider or State or local public health officials recommend you take one**."

The explanation of the change was to put an emphasis on testing people who are displaying symptoms of COVID-19 and those in long-term care facilities and nursing homes and people who may be particularly vulnerable to the infection (Sheridan, 2020).

The changes were questioned by a number of government officials and public health experts who feel that it will be harder to isolate people who are spreading SARS-CoV-2 because people are infectious before they experience symptoms, and some people do not have noticeable symptoms at all, but they can still transmit the virus (Branswell and Sheridan, 2020). Central to the issue is that the guidance was crafted by the White House coronavirus task force rather than the CDC or other parts of the government normally tasked with assessing scientific information to inform policy decisions.

Pharmacists can Give Children Immunizations

In an effort to keep levels of immunization for childhood vaccinations at appropriate levels, the Department of Health and Human Services has used its emergency powers to grant pharmacists the authority to administer shots to children (Stobbe, 2020). The CDC has reported that orders for vaccinations at doctor's offices were much lower in March and April than the rates observed in previous years due to office closings or restriction in available appointments. There were 28 states that already allowed pharmacists to administer vaccinations to children, and the authority has been granted in the remaining 22 that had restrictions or prohibitions. The new regulations do not allow pharmacists to administer shots to children under the age of three.

Contact Tracing Scams

Both state and federal officials are investigating phone scams with people posing as contact tracers (Appleby, 2020).

> **The fake calls include requests for credit card or bank information, which is not part of a legitimate contact tracing call.**

Legitimate contact tracing calls may be preceded by a text message to notify the individual of an upcoming call from the health department. Texts from the health department do not include links, and communications from others may include malware to infect your phone or computer. The tracers confirm some personal information, including address and date of birth, in order to make sure they have reached the right person and that they do not disclose potentially private information to the wrong person. The name of the person you were exposed to will not be disclosed in order to protect their privacy as well.

> **If in doubt, call back your local health department, using the published phone number, if you are being contacted for potential exposure to COVID-19.**

Reinfection with SARS-CoV-2

The extent of immunity to SARS-CoV-2 after initial infection is a key question that has yet to be definitively answered about the virus. There were two descriptions that help to clarify the response to a second exposure to the virus.

A preprint from researchers at the University of Washington School of Medicine in Seattle, Washington describes an outbreak on a fishing vessel (Addetia et al., 2020). There were a total of 122 people on the ship, and all tested negative for COVID-19 before departure by RT-PCR for active infections and using serological tests to determine previous exposure. Serological and viral RT-PCR testing before departure and repeat testing after return to shore was available for 120 of the 122 persons on board over a median follow-up of 32.5 days with a range of 18.8 to 50.5 days. Six people had positive serological tests, but follow-up investigations of the samples taken before the trip showed that only three had neutralizing antibodies to the virus.

One of the people on the boat reported symptoms 16 days after departure and was subsequently hospitalized. Of the 120 people with repeat testing after return of the boat, 104 had a positive RNA test, showing they had an active infection.

> **None of the crewmembers identified as having neutralizing antibodies before the trip had a positive test or reported any symptoms during the trip.**

The attack rate of infection on the ship was 85.2% based on 104 of 122 individuals becoming ill.

> **When the probability of contracting the virus on the ship was analyzed, the researchers found there was a statistically significant association between the presence of neutralizing antibodies from a prior infection and protection against re-infection**

Another report was published in the journal *Clinical Infectious Disease* of a 33-year-old man in Hong Kong who was found to have contracted two different types of SARS-CoV-2 142 days (or 4 and half months) apart (To et al., 2020). During the first infection, the individual reported cough and sputum, sore throat, fever and headache for 3 days at the time of diagnosis. As was protocol, he was hospitalized, but he did not require treatment, and his symptoms subsided by the time he was admitted. The second infection was asymptomatic and was identified through screening at the Hong Kong airport after arrival from Europe. The genetic testing of the virus from each episode confirmed that the virus detected from the second infection was a different strain from the first. There is no clinical difference between the strains, but the RNA sequences differ and can be differentiated.

> **While reinfection occurred, the second case of COVID-19 was asymptomatic, suggesting that the immune response may provide protection if re-exposure occurs**.

A second report of re-infection with SARS-CoV-2 was reported in a 25-year-old resident of Reno, Nevada (Tillett, 2020). The report was published as a preprint. The initial infection occurred in March with symptom onset on March 25, which included sore throat, cough, headache, nausea, and diarrhea. Diagnosis was made at a community testing event, and recovery was determined by symptom resolution on April 27 and two negative PCR-based tests in May with the last test on May 26.

On May 31, 48 days after previous symptom resolution, the individual felt ill again with fevers, headache, dizziness, cough, nausea, and diarrhea, but an x-ray showed no lung involvement. On June 5, the individual was found to be hypoxic at an appointment with a primary care physician and sent to the emergency room where they were tested for COVID-19. Symptoms included myalgia, cough and shortness of breath with a need for supplemental oxygen. PCR-based testing showed an active SARS-CoV-2 infection, and serological testing on June 6 indicated the presence of IgG and IgM antibodies against SARS-CoV-2.

Genetic sequencing of samples of virus from the two time periods indicate that there were differences suggesting infection at two different times with different viruses. It was determined that the viruses were part of the same clade (from a common "descendent"), but were different enough that normal mutation rates could not have produced the new virus in one person in the time period between symptoms.

Based on the information from the case study, the authors conclude that initial exposure to the SARS-CoV-2 virus may not result in a level of immunity that is 100% protective for all individuals, but with a single case it is not possible to tell yet if this is a rare event.

SARS-CoV-2 Mutation

Overall, the mutation rate of SARS-CoV-2 has been shown to be very low, with 99.9% genetic sequence similarity between viral samples from different parts of the world (Jalandra et al., 2020). However, researchers in Singapore recently published a report in the *Lancet* about a mutated form of the virus that has a milder clinical course than the version of the virus in most parts of the world (Young et al., 2020). The mutated version of SARS-CoV-2 has 382 genetic units, called nucleotides, removed from the genome. The mutation has been named Δ382 (pronounced delta 382), and it occurs in a region of the SARS-CoV-2 genome called open reading frame 8 (or ORF8). The biological function of the protein produced from ORF8 is currently unknown. Δ382 has been observed in Singapore, Taiwan, Bangladesh, Australia, and Spain, but after March it has no longer been detected circulating in the population.

In the study, 131 participants with PCR-confirmed COVID-19 were screened for Δ382. The study took place between January 22 and March 21, and 70% had the normal, full-length version of the virus, 22% had only the Δ382 variant, and 8% a mixture of the two. Individuals with the mutated form of the virus were less likely to develop hypoxia requiring supplemental oxygen than those with the full-length form (0% compared to 28%, respectively).

Based on this information and previous studies on other coronaviruses, the authors conclude that ORF8 is a hotspot for coronavirus mutation, leading to a clinical effect of milder infection with less systemic release of pro-inflammatory cytokines and a more effective immune response to SARS-CoV-2.

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