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Medical Intelligence Report

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Topic: Update on COVID-19 Research

Pfizer Vaccine (BNT162) Clinical Trial

Pfizer and its partner BioNTech published a press release that describes the first interim analysis of the Phase 3 trial of BNT162, which is their vaccine candidate for the prevention of COVID-19 (Pfizer, 2020). The study has enrolled 43,538 participants from several different sites around the world with half of the volunteers receiving the vaccine and half receiving a placebo in the form of a saline injection. The analysis was performed, as was described in the study's protocol, when there were 94 confirmed cases of COVID-19 reported in the participants.

The procedure for the protocol includes six planned visits to collect information and administer the vaccine or placebo as well as unplanned visits with study personnel as needed if participants develop symptoms of COVID-19 (Pfizer, C4591001, 2020). After being screened for inclusion in the study, the participants were randomly assigned to receive either the vaccine or the placebo, and both the participants and staff who administer the vaccine and assess outcomes are not aware of who has received the vaccine and who has received the placebo.

There were several important points about the participants included in the trial. First, there is a wide range of age groups from 12 years of age and older with a minimum of 40% of participants over the age of 55. Including both young adults and older individuals is important because young adults are more likely to have an increased number of contacts outside their household and older individuals are at higher risk for severe outcomes and are often excluded from early trials. There was also a conscious effort to expand the racial and ethnic diversity of participants in the trial, which led to 42% of global participants and 30% of U.S. participants reporting racially and ethnically diverse backgrounds.

The first and second injection occur between 19 and 23 days apart. Observation visits are then scheduled at one month, six months, 12 months, and 24 months after the second injection. Participants were instructed to contact study personnel if they developed symptoms of COVID-19.

The initial list of COVID-19 symptoms used included the presence of at least one of the following symptoms

- Fever
- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste or smell
- Sore throat
- Diarrhea
- Vomiting

Additional symptoms were updated as more was learned about COVID-19, and symptoms of fatigue, headache, nasal congestion or runny nose, and nausea were later added.
Testing for SARS-CoV-2 was performed using PCR-based tests within four days before or after the symptomatic period at the central laboratory associated with the trial site or at a local testing facility using an acceptable test if travel to the central laboratory was not possible.

For those participants without symptoms, blood samples will be tested for the presence of antibodies to SARS-CoV-2 that are collected at the regularly scheduled observation appointments. Four different antibody tests will be conducted to screen for previous SARS-CoV-2 infection.

Based on the results of the interim analysis, the researchers found that participants who received two doses of the vaccine had 90% fewer symptomatic cases of COVID-19 than those who received the placebo.

This is well over the efficacy rate that was used as a target for the trial, which was between 60% and 70%. The safety profile of the vaccine was good, but there were some side effects, including aches and fevers after the injection. The researchers will continue to collect data, and a final analysis of the trial will be performed when there are 164 confirmed cases of COVID-19. Later analysis over the entire 24 month period will also be performed.

Pfizer has stated that they will apply for Emergency Use Authorization of the vaccine in the third week of November, when half of the patients in the study have been observed for safety issues for at least two months following their second dose. This time point was set up before the trial began in coordination with the FDA (Herper, 2020).

As usual, there are still unanswered questions about the vaccine, including

- Whether the vaccine prevents severe cases
- If the vaccine prevents people from asymptomatic infection
- How long the vaccine will protect against infection by the virus
- How to facilitate distribution because the vaccine must be stored at very low temperatures (-80° C)

Potential COVID-19 Treatments

LY-CoV555 Antibody Treatment from Eli Lilly

Researchers investigating the efficacy of Eli Lilly's neutralizing antibody called LY-CoV555 published their interim analysis from a Phase 2 clinical trial in the *New England Journal of Medicine* (Chen et al., 2020). The company is planning on using the name bamlanivimab as the investigations continue. In the trial, 452 participants were randomly assigned to a group to receive a single intravenous infusion of the antibody LY-CoV555 in one of three doses (700 mg, 2800 mg, or 7000 mg) or a placebo infusion. The participants had been recently diagnosed with mild cases of COVID-19 and did not require hospitalization. The researchers were assessing the ability of the treatment to reduce the amount of virus produced, lessen symptoms, and prevent hospitalization.

It was found that treatment with the 2800-mg dose of LY-CoV555 led to a 3.4-fold reduction in the amount of viral RNA that was detected compared to participants receiving the placebo. The lowest and largest doses led to much smaller decreases in viral RNA that were considered not clinically significant. On days 2 to 6, the participants who received LY-CoV555 had a slightly lower severity of symptoms than those who received placebo. The percentage of participants who had a COVID-19–related hospitalization or visit to an emergency department was 1.6% in the LY-CoV555 group and 6.3% in the placebo group. When the participants with high risk were evaluated separately (e.g. those over 65 years of age or those with a BMI in the obese range, there was a larger magnitude in the difference with 4% requiring hospitalization or emergency room treatment in the group receiving the antibody and 15% in the group who received the placebo.

No one taking LY-CoV555 had a serious adverse event, and one person in the placebo group reported a serious adverse event. The researchers concluded that one of three doses of LY-CoV555 accelerated the decline in viral load over time, while the other doses did not have a large effect by eleven days after treatment.

> **One of the researchers involved stated that "These data indicate that the treatment is safe. The patients who received LY-CoV555 had fewer hospitalizations and a lower symptom burden than those who received placebo, with the most pronounced effects observed in high-risk" groups.**

The NIH also announced termination of a similar trial investigating the effects of LY-CoV555 in hospitalized individuals due to a lack of effect (NIH, 2020 and Paulsen, 2020). The trial had been paused on October 13, due to a possible adverse event. There were no safety issues identified when the events were closely examined, but the researchers also found that there was a lack of clinical benefit for hospitalized patients. The researchers postulate that the lack of effect in those needing hospitalization is due to a longer course of infection, more severe symptoms, and receiving different treatments than those who do not require treatment in the hospital.

Based on the outcomes, the researchers suggest that LY-CoV555 may prevent the progression of disease in individuals with early-stage COVID-19. A Phase 3 trial is being organized to determine the effect of antibody treatment in residents and staff of long-term care facilities.

Assessment of Time Until Infection Levels Change with Non-Pharmaceutical Interventions

The time interval between changes in community-wide interventions such as closing school, banning large gatherings, or closing non-essential businesses has been estimated based on the incubation time and other characteristics of SARS-CoV-2, but researchers have now been able to use reported outcomes to assess the time frame for an effect to manifest (Li et al., 2020).

It took a median of 8 days following the introduction of non-pharmaceutical interventions to observe 60% of the maximum reduction in the reproduction number. The reproduction number is the expected number of COVID-19 cases directly cause by a single infected person. When interventions were lifted, it took longer to observe an effect. It took a median of 17 days after relaxation to reach 60% of the maximum increase in the reproduction number. A combination of reopening schools, lifting bans on public events, lifting bans on public gatherings of more than ten people, lifting requirements to stay at home, and lifting internal movement limits led to an increase in the reproduction number by between 11% and 25% on day 28 following the change.

Overall, the researchers describe a delay of between one and three weeks before the effects of lifting or implementing restrictions could be observed.

COVID-19 Incidence in Non-Healthcare-Based Essential Workers

In order to evaluate the incidence of COVID-19 in essential workers that do not work in healthcare, researchers assessed the occupational history and COVID-19 status of workers at a single retail grocery store in Massachusetts (Lan et al., 2020). During the study, 104 workers were tested for COVID-19 with PCR-based testing, and additional information was obtained from questionnaires about anxiety and general health status.

Of those tested, 20% were found to be positive, and 76% of the individuals with a positive test were not experiencing symptoms.

Workers who had direct contact with customers were five times as likely to test positive.

Symptoms of anxiety were identified in 24% of the workers, and 8% had symptoms of depression. Those who were able to practice social distancing consistently at work had lower risk of anxiety or depression. Use of public transportation also increased the likelihood of anxiety or depression compared to workers commuting by foot, bike or private cars.

Infection Rates and Infection Fatality Rates

Researchers performed an analysis of age-specific mortality in relation to the presence of antibodies to better understand the differences in infection and fatality from SARS-CoV-2 between countries and in different population groups (O'Driscoll et al., 2020). Based on the analysis, they found that there is a consistent risk of death for individuals under 65 years of age around the world with little variation between different countries. However, in older individuals, there is a larger amount of variation in the risk of death based on region.

The infection fatality rate was calculated based on age and ranged from 0.001% for those between the ages of five and nine years to 8.29% in individuals over the age of 80. The infection fatality rate for those over the age of 80 ranged from 2.49% to 15.55% between different national-level studies. There was a mean increase of 0.59% in the infection fatality rate for each five years of age. There was also a large difference in the infection fatality rate between older men and women with an overall fatality rate of 10.83% for men over 80 years of age and 5.76% for women over 80 years of age.

The nationwide infection fatality rates were found to be different in countries that have different population demographics. For example, Japan has a high proportion of older individuals, and the infection fatality rate was 1.09%. Kenya, on the other hand, has a larger younger population, and the infection fatality rate was 0.09%.

Of the 45 countries included in the analysis, representing 3.4 billion people, the researchers estimate an average of 5.27% of the populations had been infected by September 1. The values range from 0.06% in South Korea to 62.44% in Peru.

The infection fatality rate and number of infected individuals in nursing homes or long-term care facilities is much higher. The analysis indicates an infection fatality rate of 22.25% in French nursing homes with 7.28% of the nursing home population infected. The infection rate is 1.70 times that of the general population as of September 1.

Improvements in Survival of Individuals Receiving Critical Care

A study of the outcomes of individuals receiving critical care for COVID-19 in England indicates that there has been a substantial improvement in survival of this group (Dennis et al., 2020). The study investigated 21,082 individuals who were treated in the high-dependency unit or intensive care unit between March 1 and June 27. Records of people treated were accessed through the COVID-19 Hospitalisation in England Surveillance System database.

The survival rate 30 days after hospital admission was the lowest in late March with 71.6% survival in high-dependency units and 58.0% in intensive care units. By the end of June, survival had improved to 92.7% in high-dependency units and 80.4% in the intensive care units. The improvement was not associated with differences in age, sex, ethnicity, or major comorbidity burden of the admitted individuals.

The authors stated that changes in COVID-19 disease severity at admission, patient selection for critical care management, critical care treatment, hospital capacity, and COVID-19 testing could explain the differences.

The timing of the change also corresponds with the start of the RECOVERY clinical trial that investigated the use of dexamethasone, cytokine lowering drugs, and convalescent plasma. Increases in the use of these treatments may have contributed to the better survival rates, but the authors were not able to access specific medications used from the database. Therefore the effect of specific medications could not be included in the analysis.

There was also a change in occupancy levels of hospitals in England between the two time periods. There is a well-established decline in patient-specific outcomes that has been observed when hospitals reach thresholds of unsafe occupancy levels. Based on the available data, the authors could not determine if improvements in the quality of care led to improvements in survival.

Predictors of In-Hospital COVID-19 Mortality

Researchers have performed a systematic review of published articles up to July 27 to analyze the individual characteristics that contribute to death from COVID-19 after hospitalization (Mesas et al., 2020). There were 60 studies identified that included 51,225 people from 13 countries. The researchers investigated the association between symptoms of COVID-19, chronic conditions, and the results of blood tests during hospitalization.

There were some characteristics that were associated with worse prognosis in all age, sex and health status subgroups. For instance, difficulty breathing, or dyspnea, was associated with poorer prognosis for all individuals, but this was the only symptom of COVID-19 that had a correlation. Higher mortality risk was found for patients who smoked and those with pulmonary disease, cardiovascular disease, cerebrovascular disease, kidney and liver diseases, hypertension, diabetes, and malignancy. Among laboratory parameters, the highest mortality risk was observed for routine blood tests such as lymphocytes (B and T cells), leukocytes (all immune cells or white blood cells), neutrophils (cells involved in the inflammatory response), and platelets (cells that help with clotting) as well as clotting indicators (D-dimer and prothrombin time), liver function (albumin, total bilirubin, aspartate and alanine transaminase), kidney function (urea nitrogen and creatinine), and inflammatory factors (CRP, IL-6, LDH, procalcitonin, ferritin and cardiac troponin).

There was also a difference in the characteristics based on age. In younger individuals, there was a higher mortality risk when dyspnea and a history of smoking were present when compared to older individuals. The mortality risks were also higher when younger people had chronic conditions compared to older individuals. The most important mortality predictors in studies with older patients were liver function indicators, kidney function indicators, and inflammatory factors such as C-reactive protein, LDH, and ferritin.

Based on their results, the authors were able to make some suggestions about possible characteristics that are important for certain groups.

- Trouble breathing is a common symptom of COVID-19 in hospitalized individuals, but when evident in younger individuals, special attention is necessary.

- When low hemoglobin levels were present in individuals otherwise typically at low risk for poor outcomes, or younger and healthier people, the prognosis was worse. Small reductions in hemoglobin may identify those with the lowest chance of survival among these patients.

- The contribution of chronic conditions to a poor prognosis for is higher for young patients and men.

- Older COVID-19 patients had higher potential for more serious organ damage caused by SARS-CoV-2 infection, and specific blood tests that indicate liver damage, kidney damage, and increased inflammation could be used for early identification of elderly patients with worse prognosis.

Cardiovascular Effects

There has been a high number of individuals with COVID-19 with evidence of heart damage based on the presence of heart-related enzymes present in blood-work, which is referred to as myocardial injury. Researchers have correlated evidence of heart damage from blood-based markers with visual evidence of structural abnormalities in the cardiovascular system (Giustino et al., 2020). In the study, the researchers assessed 305 individuals who were hospitalized for COVID-19 in 7 hospitals in New York City, New York and Milan, Italy.

There was evidence of myocardial injury in 62% of the individuals. Potential cardiac damage was detected using transthoracic echocardiographic (TTE) and electrocardiographic evaluation. Compared to those without evidence of myocardial injury, there was a higher rate of major abnormalities, including left ventricular wall motion abnormalities, global left ventricular dysfunction, left ventricular diastolic dysfunction grade II or III, right ventricular dysfunction, and pericardial effusions. Individuals without myocardial injury had an in-hospital mortality rate of 5.2% while those with evidence of myocardial injury had an in-hospital mortality rate of 18.6%. Those with myocardial injury and evidence of structural abnormalities in the heart had an in-hospital mortality rate of 31.7%.

In the individuals assessed with TTE, cardiac structural abnormalities were present in nearly two-thirds of patients with evidence of myocardial injury. Myocardial injury was associated with increased in-hospital mortality particularly if echocardiographic abnormalities were present.

> **In a press release describing the article, the authors state that heart damage is prevalent among patients hospitalized with COVID-19 and is associated with higher risk of mortality.**

Along with identifying individuals in the hospital who may require close observation for cardiac complications, the research also allows for identification of individuals who may be at higher risk for long-term complications (Mt. Sinai, 2020).

Outbreak from Transmission on a Flight

There is increasing evidence of transmission of SARS-CoV-2 on long airplane flights. The latest report describes an outbreak of 59 cases that were traced back to a seven hour flight to Ireland over the summer (Murphy et al., 2020).

Importantly, the airplane was only at 17% capacity, and there was between a 9.8% and 17.8% attack rate on the flight.

Transmission while on the flight was confirmed based on genetic sequencing of the virus. There were five asymptomatic or pre-symptomatic index cases on the flight that originated from three different continents. After the flight, there is evidence of spread to an additional 46 people who were not on the flight.

Prolonged Shedding of Infectious Virus

Researchers identified an individual with COVID-19 who shed infectious virus for much longer than the typical eight days observed for most infections (Cell Press, 2020 and Avanzato et al., 2020). The individual was being treated for leukemia and was immunocompromised, and it was determined that she was infected with the COVID-19 for at least 105 days and infectious for at least 70, while remaining asymptomatic the entire time. The physicians treating the woman noticed that she had tested positive with PCR-based testing for an extended length of time, and they began testing to determine if she was still shedding infectious virus.

They found that infectious virus continued to be present for at least 70 days after the first positive test.

The rare extended infection is thought to have occurred because of a lack of an immune response. Blood tests indicate that no antibodies against SARS-CoV-2 were produced over the length of the infection. There was no evidence of mutations in the virus genome over the course of the infection.

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